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A STUDY OF THE PANCREATIC DUCT SYSTEM IN MAN BY THE USE OF VINYL ACETATE CASTS OF POSTMORTEM PREPARATIONS

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In recent years there has been growing interest in the duct system of the pancreas as concerns its relationship to pancreatitis. Rich and Duff in 1936 first stressed the importance of duct metaplasia as a source of obstruction in the pancreas. Wainright, Berens, and Nemir recently have cited cases involving duct metaplasia and duct calculi and have described dilatation of the duct system. It is postulated, with the mechanism of obstruction, that there would be rupture of terminal ductules or pancreatic acini with escape of pancreatic juice into the pancreatic substance, activation of trypsinogen to trypsin, and hemorrhagic digestion of the gland which could secondarily involve adjacent parenchyma.

Starting in retrograde manner from the papilla of Vater, the following pathologic findings have been variously described as the cause of pancreatic duct obstruction and pancreatitis: (1) edema of the papilla of Vater associated with edema of the duodenal mucosa causing obstruction of the duct of Wirsung and pancreatitis (viz., in alcoholics); (2) stone in the distal common duct at or near the papilla causing contiguous pressure obstruction of the duct of Wirsung; (3) spasm or fibrosis of the sphincter of Oddi; (Here again contiguous involvement of the duct of Wirsung could well result in pancreatic duct obstruction.) (4) duct metaplasia at any level of the pancreatic tree; (5) calculi within the pancreatic duct system.

Little consideration has been given in the past to the role of segmental duct obstruction with rupture of collecting ducts or tertiary ductules. These drain only a segment of the gland and their rupture could then trigger disease of the adjacent gland. The role of relative or partial obstruction, physiologic obstruction, with an actively secreting gland and a tortuous or angulated duct system has not been explored. Inspissation of pancreatic secretion in the ducts of a "dried out" starved gland in a fasting individual, later subjected to the pressure of a hypersecreting gland after a

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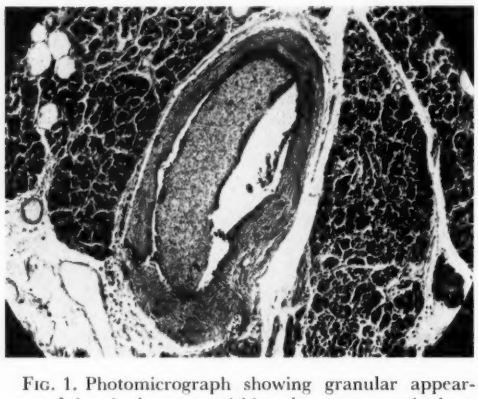

FIG. 1. Photomicrograph showing granular appearance of the vinyl acetate within a large pancreatic duct. ×57.

heavy meal, could well result in rupture of acini and explain the sequence of events in the case report of McDermott and associates.

If intrinsic pancreatic duct obstruction is to be indicted in the pathogenesis of pancreatitis, it is long overdue to review and refine the anatomy of the duct system. When this study was initiated, it was anticipated that there would be an opportunity to study the variations in the anatomy of the pancreatic duct system in fatal cases of pancreatitis as well as in the general postmortem population. Unfortunately, autopsy has not been performed in a single fatal case of hemorrhagic pancreatitis at this center since the study was undertaken. There have been a few cases of chronic pancreatitis. Notwithstanding, the data obtained from this study of 143 postmortem preparations represents a control series for later studies of the same kind in cases of fatal hemorrhagic pancreatitis. Of interest have been the observations of variations in the duct system associated with diseases which have clinically some relationship to pancreatitis, i.e. cholelithiasis and cholecystitis, cirrhosis, and alcoholism. These will be indicated later in this report.

METHODS

In the past, several different methods have been used to study the anatomy and arrangements of the pancreatic ducts and common bile duct. The earliest investigations by Opie (16) and Baldwin made use of the gross dissection technique, and Baldwin also used dye injections. Kleitsch in 1955 used several methods. He first fixed specimens in formalin and then used gross dissection, but abandoned this method when it did not seem possible to trace the accessory duct to the minor papilla with any degree of certainty. He then attempted to demonstrate the ducts by injection of vinyl plastic and macerating the gland substance with concentrated hydrochloric acid. This method was abandoned because the vinyl plastic was distorted when the gland was macerated. He tried roentgen studies with success, but later abandoned them because of limitation by two dimensions. He then injected latex or vinyl plastic into the pancreatic system, whereupon the gland was dehydrated with acid alcohol and impregnated with methyl salicylate.

None of the foregoing techniques was completely satisfactory, and for better definition we chose the vinyl acetate method of Patel and Burton in order to visualize the finer ramifications of the pancreatic ducts with permanent specimens for study.

Vinyl acetate or latex was injected into 143 human pancreases obtained from routine autopsy material. The vinyl acetate is a plastic substance dissolved in acetone and sold in 12 per cent solution. Latex, which was found to be less useful than vinyl acetate because of its nonrigid character, was used in only a few of the preparations.

The autopsy material was provided by patients of widely varying ages and with many different disease processes. The age distribution ranged from 9 months up to 94 years, and a variety of disease states were encountered including disorders of the gallbladder and liver, alcoholism, diabetes mellitus, chronic calculous pancreatitis, and pancreatic neoplasms. No case of acute hemorrhagic pancreatitis was available for study in this series.

At the time of autopsy the pancreas was

removed as a block of tissue including the antrum of the stomach and the entire duodenum and the terminal common duct. The duodenal lumen was opened and washed, and the entire specimen was wrapped and placed in the deep freeze until the injection could be carried out. No incisions were made in the pancreatic tissue at this time. The majority of the specimens were obtained within 6 hours of the time of death but excellent preparations were occasionally obtained from 24 to 36 hour postmortem specimens. It was also noted that the specimens could be held frozen indefinitely—several months elapsing in some cases before the injection was carried out.

At the time of injection the specimens were thawed in warm water and the major and minor papillae were identified. The injections were carried out through an 18 gauge cannula, utilizing one of three ports, i.e., (1) the entrance of the duct of Wirsung into the ampulla, (2) the main duct in the pancreatic tail after partial transection of the gland, and (3) the common bile duct after clamping the duodenal mucosa at the papilla. This last portal was found to be most satisfactory since it facilitated identification of the ducts of Wirsung and Santorini in relationship to the common bile duct. Occasionally, as will be pointed out later, it was necessary to utilize 2 ports to obtain a satisfactory injection. The plastic substance was injected rapidly by means of a 10 cubic centimeter syringe and the injection was stopped when regurgitation of the material was noted. Three cubic centimeters were usually needed to obtain a satisfactory specimen; some glands, however, required 6 to 8 cubic centimeters. Overdistention of the duct system with rupture of the minute subsurface ducts was occasionally encountered.

After the injection was completed, the specimen was trimmed so that only the pancreas remained and an outline of the gland was traced to indicate its size. Blocks of tissue were then removed from the distal body and tail, fixed in formalin, and processed for microscopic tissue sections. The plastic material was readily identifiable microscopically in that it stained a brilliant crimson in the usual hematoxylin and eosin section (Fig. 1). It was thus possible to correlate histopathology with the gross observation of the duct system.

FIG. 2. Vinyl acetate cast of the pancreas embedded within bio-plastic.

The injected pancreatic glands were next corroded in either 10 per cent potassium hydroxide or hydrochloric acid, respectively, dependent upon whether vinyl acetate or latex was used. It was found that this process could be hastened by placing the corroding specimen in the incubator at 37.5 degrees C. After 24 hours it was usually possible to lift the cast away from the digested soft tissues.

In selected specimens the pancreatic arterial system was injected in association with the duct system. Separate colors were used for the vessels supplied by the celiac axis, the superior mesenteric branches, and for the duct system.

Some shrinkage occurred with the use of vinyl acetate but this did not interfere with the value of the cast preparation. The specimens which were somewhat friable were best handled with eye forceps during their study. A permanent specimen can be obtained by embedding the entire cast in bioplastic (Fig. 2).

EMBRYOLOGY

One must review the embryologic development of the pancreas to clearly understand the variants that will be described in this study. The pancreatic duct system has two separate sites of origin: (1) a smaller ventral bud that arises from the common bile duct and (2) a larger dorsal bud that arises independently from the duodenum, cephalad to this. The descending portion of the duodenum in its development rotates on its long axis and the ventral bud with the common bile duct comes to lie posterior to the dorsal bud. The head and uncinate process of the pancreas, so-called Wirsung system, are derived from the ventral bud, whereas the body and tail are contributed by the dorsal bud, the Santorini system. A connecting segment joins the ventral to the dorsal duct, and the duodenal derivative of the dorsal development tends to atrophy. In rare cases, only the Santorini system (from the dorsal bud) persists and becomes the main duct system. Any opening separate from the papilla of Vater must be a derivative of the Santorini system as Wirsung in its development must relate to the common bile duct, and cannot emerge separately from it.

RESULTS

On the basis of methods previously used, there has been much confusion concerning the normal anatomy of the human pancreatic duct system. Statistics relating to the common emergence of Wirsung and the common bile duct vary from 4.5 to 98.3 per cent. The duct of Wirsung and the common bile duct have been described with separate openings at the papilla in from 8 to 60 per cent of cases studied, and a separate pancreatic papilla has been reported in from 1.7 to 20 per cent of cases. One phase of our investigation was to attempt to clarify this anatomy.

In this study, the various relationships of the duct of Wirsung to the common bile duct, the ampulla of Vater, and the duct of Santorini are illustrated in Figures 3 to 6. Figure 3 demonstrates the variants of development of the duct of Santorini. Figure 3A indicates the number of specimens (48.5 per cent) in which the duct of Santorini was not visualized. A duct of Santorini was present and opened into the duodenum at the minor papilla as in Figure 3B in 43 of 130 specimens (33.1 per cent). In 10 specimens (7.7 per cent) a duct of Santorini was observed to be present, but not communicating with the duodenum, as in Figure 3C, and this arrangement was termed "blind Santorini." This observation was based entirely upon the failure to see regurgitation of vinyl acetate at the minor papilla upon injection in spite of a definite Santorini duct being identified in the cast specimen. Whether the minor papilla is patent or not in these instances could not be proved by our technique.

In this study, the most consistent arrangement of the duct of Wirsung and the common bile duct, as illustrated in Figure 3A, consisted of a confluence of the two ducts within 2 to 3 millimeters of the papilla of Vater—a common channel, albeit a foreshortened one. This is in contrast to the arrangement shown in Figure 5 in which the common channel is more evident.

Figure 4 illustrates 8 of the 130 specimens (6.2 per cent) in which the duct of Wirsung and the common bile duct open independently at the papilla of Vater. Five specimens show no duct of Santorini, as in Figure 4A; 2 specimens demonstrate a patent duct of Santorini as in Figure 4B; and 1 specimen falls under the category of "blind Santorini," Figure 4C.

Figure 5 shows another variation of the duct of Wirsung in which it opens into the common bile duct from 5 to 15 millimeters proximal to the papilla. This is the often cited arrangement in the literature of pancreatitis in which the "common channel theory" is invoked.

Figure 6 shows the rarer arrangements of the pancreatic ducts. Embryologically, the ventral pancreas may fail to develop and leave the duct of Santorini as the only duct

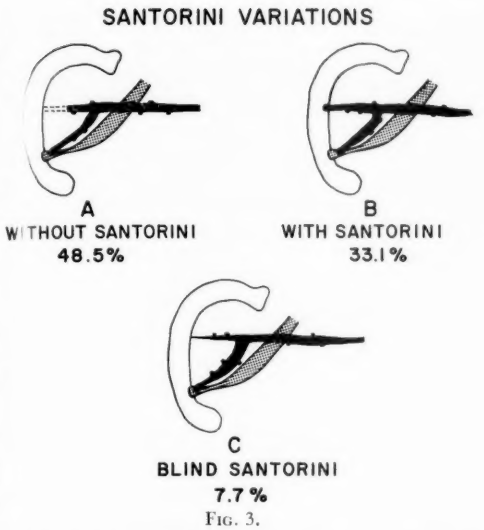

FIG. 3.

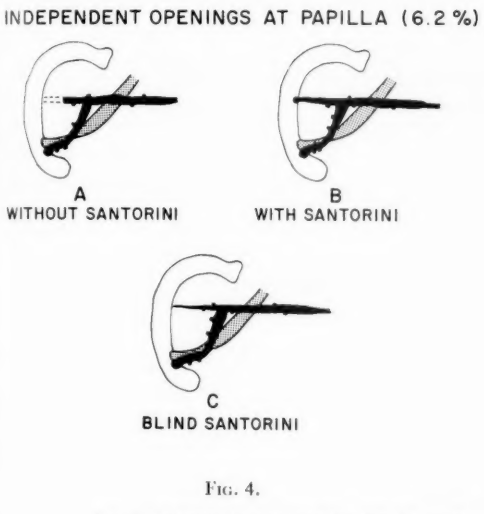

FIG. 4.

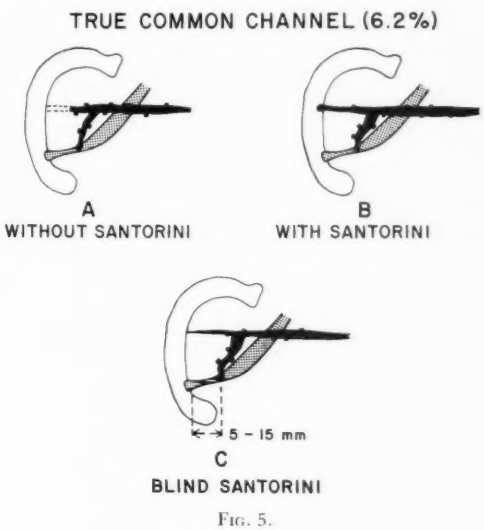

FIG. 5.

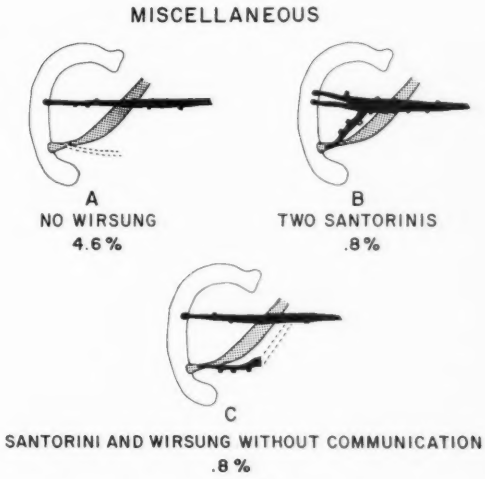

FIG. 6.

FIG. 3. Schematic drawing showing the types and frequency of Santorini variations encountered in this study. Note the relationship of Wirsung and the common bile ducts as they enter the duodenum.

FIG. 4. Schematic drawing showing the frequency with which we encountered separate openings for Wirsung and the common bile ducts.

FIG. 5. Schematic drawing showing the frequency of the so called common channel in this series.

FIG. 6. Schematic drawing showing miscellaneous rare arrangements of the Santorini and Wirsung systems.

(Fig. 6A). Figure 6C shows the 1 specimen in which the duct of Wirsung is present but fails to communicate with the dorsal pancreas. One specimen (Fig. 6B) shows duplication of the distal duct of Santorini with 2 minor papillae in the duodenum. It was evident in almost all of the specimens that the dorsal development (Santorini) contributed the main duct in the body and tail whereas Wirsung contributed the entrance

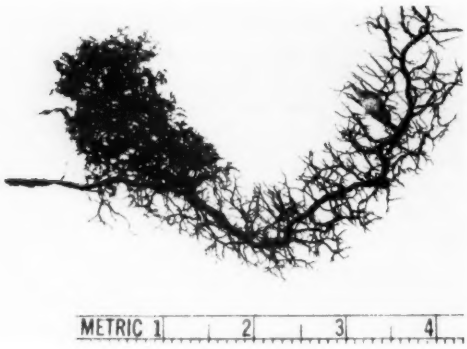

FIG. 7.

FIG. 8.

FIG. 7. Cast specimen from a 5 year old child. Both Santorini and Wirsung outlets can be seen (Santorini is the smaller upper outlet at the left of the illustration).

FIG. 8. Cast from a 42 year old man. Note the twisting of the main duct and the blunted terminal ducts. No Santorini outlet was present.

into the papilla and the drainage from the head and uncinate process of the gland.

It was of note that our results as tabulated are statistically in high accord with the studies by Millbourn and Hjorth whereas other investigators have shown a wide range of variation.

In addition to the Wirsung-Santorini relationships, the duct cast was carefully studied to elucidate information on the primary, secondary, and tertiary duct patterns. These can be designated as: (1) the primary duct system relating to the main drainage system running through the tail, body, and head of the gland; (2) the collecting ducts which enter the main duct from the lobules of the gland; and (3) the terminal ductules and acini. Very little information concerning this facet exists in standard anatomy textbooks, most simply stating that the primary ductules narrow as they enter the main duct and that they approach it from all sides.

In the present study an attempt was made to classify the entire injected specimen as rich, medium, or sparse. Bare areas were noted and their precise location charted. Attention was directed to the phenomena of "tapering" or presence of narrowing as the main duct was traced from the head to the tail. The main ducts were carefully studied for evidence of twisting, angulation, or unusual tortuosity, and again the precise location was charted. The age of the patient was recorded and the disease process to which the patient succumbed. Particular emphasis was placed on the presence of gallbladder and liver disease, diabetes mellitus, alcoholism, and pancreatitis. Finally, each cast was correlated with the microscopic pattern of the gland, the usual tissue block having been removed from the distal body or tail.

Very early in the study it became apparent that the degree of filling could be generally correlated with the age of the patient. In fact it was possible to estimate the age of the patient rather accurately from the cast specimen alone. The very fine terminal ductules of the 5 year old child are shown in Figure 7. This filling is most striking in the area of the head and it will be noted that there is significant tapering in this specimen. The duct pattern representative of middle age is shown in Figure 8, and the main duct shows considerable twisting and marked narrowing. Bare areas were not impressive in this specimen, although when present they were more common along the dorsal pancreatic surface. Tapering was

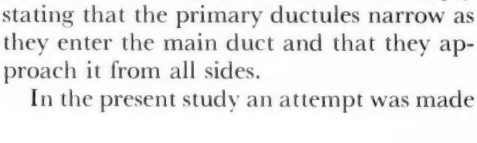

FIG. 9. Cast from a 75 year old man. The main duct is twisted and stenotic, and bareness is characteristic of the entire specimen. No Santorini outlet can be seen.

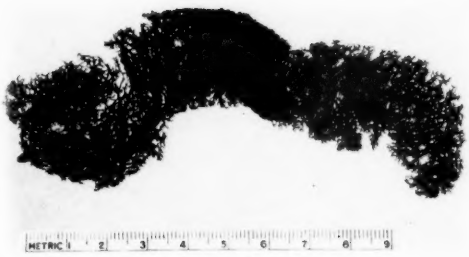

FIG. 10.

FIG. 10. Cast showing unusually fine filling in a 52 year old lady. This pattern is more characteristic of extreme youth.

FIG. 11. Higher magnification of Figure 10 showing ductular detail.

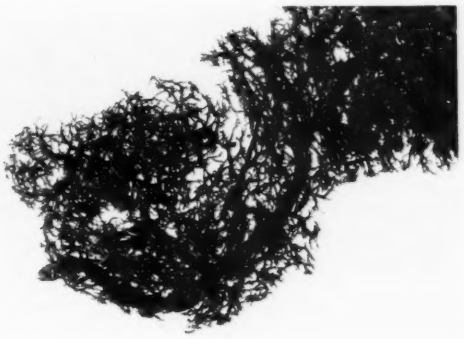

FIG. 11.

present and the fine filling of terminal ductules was not ordinarily encountered. The very sparse duct filling so frequently seen in the aged is illustrated in Figure 9. This specimen is from a 75 year old man and the main duct is twisted and gnarled and shows focal stenotic zones. The only area of terminal ductular filling is in the head, and bare areas characterize the entire circumference of the main duct. It should be stated that there were exceptions to this correlation between age and degree of filling. Such an example is shown in Figure 10. This pancreas was from a 52 year old woman and shows the very fine terminal ductular filling characteristic of youth. The fine details of this are shown in Figure 11 which is a closeup view of the head and body of this pancreas. No correlation between gross duct pattern and the sex of the patient was noted.

In almost all of the specimens there appeared to be two consistent sites of sharp angulation or narrowing of the main pancreatic duct (Fig. 12); one at the mid third of the body of the gland where it lies over the superior mesenteric vessels, and the second just beyond the head of the gland where the duct of Wirsung joins the main duct from the body and tail, usually 2 to 3 centimeters from the papilla of Vater. Occasionally there was a hairpin loop in the duct of Wirsung before its junction with the dorsal duct which could represent another site of anatomic obstruction (Fig. 13).

The cast specimen was next studied in relation to the cause of death or important associated disease. A wide range of disease processes was encountered in this study. As would be expected, patients with chronic calculous pancreatitis showed extremely poor filling. Figure 14 demonstrates a pancreas from such a patient in which filling was limited only to the head of the organ. Marked tortuosity is apparent in the main ducts of both Wirsung and Santorini. The collecting ducts draining into these main ducts were short and blunted and failed to show any evidence of terminal filling. Microscopic sections from this gland demonstrated severe diffuse fibrosis, calculi in what remained of duct lumens, and islet preservation (Fig. 15). Patients with diabetes mellitus failed to show any typical cast changes.

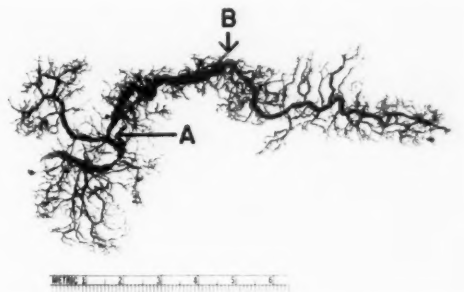

FIG. 12. Cast showing two foci of sharp ductal angulation. *A* is the point at which Santorini joins Wirsung and *B* where the gland overlies the superior mesenteric vessels.

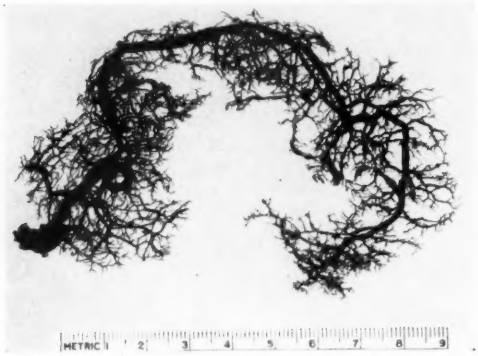

FIG. 13. Hairpin loop in the duct of Wirsung just before it joins the dorsal duct.

FIG. 14. Entire cast specimen from a patient with severe chronic pancreatitis. This was considered to be artefact before the microscopic sections of the gland were studied. The duct of Wirsung is at the left margin of the illustration.

Those specimens associated with biliary calculi formed an interesting group. In general, they were seen as sparse duct systems with few collecting ducts and rare or absent terminal ductules and acini. It must be pointed out, however, that they were in the older age groups (60 to 80 years) in which it has already been shown that sparse filling is the rule. This may well be a reflection of the increased incidence of gallstones in the older age group. Interestingly enough, however, when rich filling was observed in older individuals, gallstones were never present.

Twelve patients with Laennec's cirrhosis were included in our study, and a clearcut history of alcoholism was present in 6 of them. The average age of this group was 57 years. The pancreatic casts from these 12 individuals showed some striking similarities. As a group, they were very sparsely filled specimens and bare areas were consistently present. A photograph of the cast specimen of the pancreas of a 59 year old man with chronic alcoholism is shown in Figure 16. Although there is evidence of terminal ductular filling, the specimen is in general sparse, bare, and not representative of the degree of filling expected in this age group. A detailed analysis of the alcoholic-cirrhotic group of cases is in progress and will be reported at a later date. In this connection a recent report by Woldman and associates of a postmortem study describes 156 cases in which pancreatic fibrosis was associated with cirrhosis.

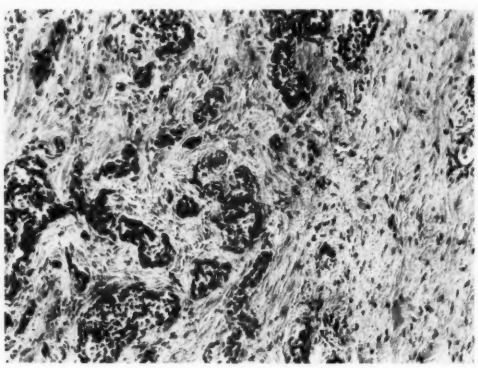

FIG. 15. Photomicrograph of the gland shown in Figure 14. There is dense fibrosis with only islet tissue remaining. ×83.

In some of the specimens it was possible to explain paucity of filling by the presence of microscopic evidence of inspissated secretions within the ducts. This type of microscopic change is illustrated in Figures 17 and 18. Changes of this type were very rarely noted in the present series but when present were associated with focal chronic pancreatitis. Duct metaplasia and interstitial chronic inflammatory cells were invariably present.

In connection with the microscopic picture one other interesting observation was made. It was obvious that the so-called "pancreatic capsule" is a mythical struc-

ture with a wide range in development. The infant capsule is a rather thick structure composed of loose connective tissue (Fig. 19). The capsules in the specimens from adults, however, may range from a thin connective tissue mantle shown in Figure 20 to the adipose pancreatic covering shown in Figure 21 from an obese adult. An awareness of the fact that there really is no true capsular structure in the terms of a splenic or renal capsule, and that acinar and ductal tissue is in contiguity with this peripancreatic connective tissue, may be of extreme importance to the surgeon.

This study has also demonstrated that it is possible to inject at the same time the arterial system and the duct system in these pancreatic specimens. For vascular injection, a block of tissue was removed which included the aorta, from the diaphragm to the renal arteries, the pancreas, and the duodenum from beyond the pylorus to the ligament of Treitz. The arteries were identified and three different colors were used to inject (1) the superior mesenteric artery, (2) the celiac axis, and (3) the pancreatic duct system as previously described. These specimens were informative in that they showed intimate vessel-duct relationships and also emphasized the variations which exist in the so-called normal arterial circulation of the pancreas. Figure 22 represents such a specimen from an individual who

FIG. 16. Cast from a 59 year old man with a history of severe chronic alcoholism. While some ductular filling is present, large bare areas characterize the specimen.

succumbed from a carcinoma of the body of the pancreas. A rich circulation within the head was found chiefly by the superior pancreaticoduodenal branches while the body and tail in the region of the tumor was practically avascular. Further studies of the vascular supply of the pancreas are contemplated.

DISCUSSION

Since Opie's (16) classical report in 1901 of a case of fatal hemorrhagic pancreatitis with a stone impacted in the papilla of Vater and a common channel between the pancreatic duct and the common duct, the literature has been replete with the attractive theory of the "common channel" with reflux of bile into the biliary tree as the cause of pancreatitis. In another case report (17), also by Opie in the same year, he suggested another explanation for the

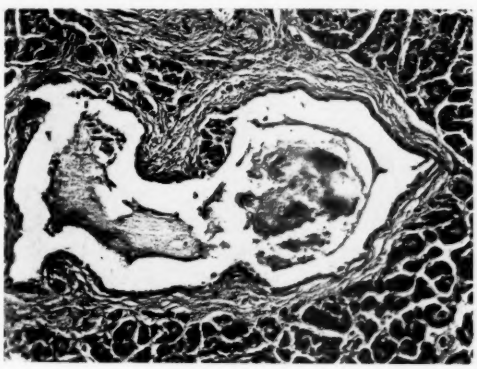

FIG. 17. Photomicrograph showing inspissated ductal secretion and several foci of squamous ductal metaplasia. ×89.

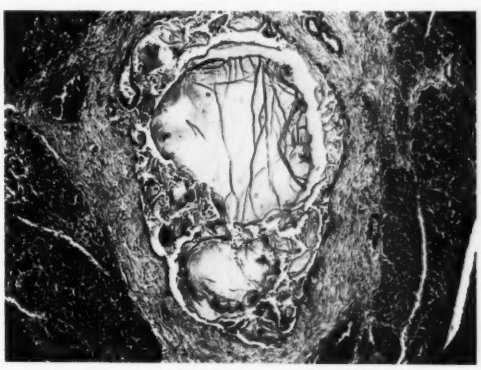

FIG. 18. Photomicrograph showing advanced stage of ductal inspissation. Material of this type frequently went on to calcification. ×57.

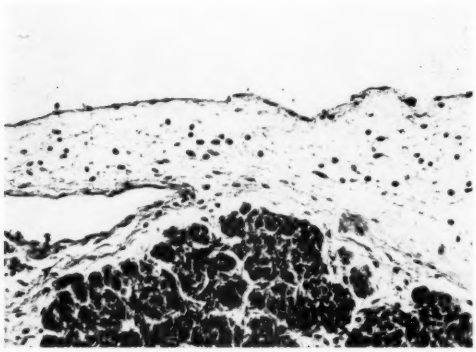

FIG. 19. Photomicrograph of the pancreatic capsule of the newborn. The loose connective tissue is myxomatous in type and rather thick. ×121.

disease, which has been since overlooked and neglected in the literature in favor of the common channel theory. In this other case, a stone in the papilla compressed both the common duct and the major pancreatic duct, causing obstruction of each system. In his own words, "since the common bile duct and the main pancreatic duct unite in the ampulla of Vater before reaching the lumen of the duodenum, changes occurring in one may produce pathologic conditions in the other with consequent lesions of the liver and pancreas." He made the point that just as obstruction of the common bile duct may cause jaundice without cholangitis, so obstruction of the pancreatic duct may cause retention of pancreatic excretory products without pancreatitis. With prescience he asked the question "when the pancreatic duct is occluded, do we find any evidence that the secretion has penetrated the surrounding tissues and produced deleterious effects?" Now 58 years later with the serum amylase test, we do have a measurement of pancreatic duct obstruction. It is conceivable that with pancreatic duct obstruction and elevated serum amylase there may or may not be pancreatitis, depending upon supervening necrosis just as with common duct obstruction and jaundice there may not be cholangitis. Byrd and Sawyers showed that in dogs, obstruction of the pancreatic ducts with transitory accumulation of pancreatic secretions in the pancreatic duct system may produce serum amylase elevation without pancreatitis.

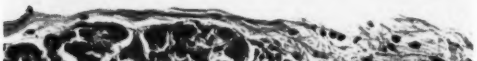

FIG. 20. Photomicrograph showing the thin acellular pancreatic capsule of a middle aged adult. ×166.

It has been generally accepted that about half of the population has a common channel but figures have ranged from the 3.5 per cent of Mann and Giordano, 18 per cent of Reinhoff and Pickrell, to the 26 per cent of Holzapfel. In the present study the main duct of Wirsung emptied into the common bile duct within a few millimeters of the papilla in almost all cases so that there was a potential merging of bile and pancreatic juice. This finding was repeatedly demonstrated in the preparations in which the injections were made into the common duct with the mucosa at the papilla being thinly clamped, and complete filling of Wirsung and the entire duct system was accomplished (Fig. 23).

In the intervening years since Opie's reports, there has been little or no good evi-

dence that reflux of bile into the pancreatic tree within the physiologic limits of bile and pancreatic secretory pressures actually occurs. Also there has been monotonous failure in cases of fatal hemorrhagic pancreatitis to demonstrate an obstructing lesion in the papilla of Vater, either a stone or fibrosis. The difficult to prove concept of spasm of the sphincter of Oddi as the obstructing mechanism has been invoked, and Doubilet and Mulholland have been the chief protagonists of the "common channel with bile reflux" theory as the prime mechanism in the pathogenesis of pancreatitis and have directed surgical therapy to correct this. However, Lium and Maddock categorically state that on the basis of anatomic evidence alone, one must conclude that in the majority of cases a retrograde flow of bile does not cause pancreatitis. Mann and Giordano have arrived at the same conclusion.

In other visceral diseases, ductal or luminal obstruction has been evident to pathologists as the prime initiating factor in disease, i.e., acute cholecystitis with cystic duct stone, acute appendicitis with impacted fecalith, and pyelonephritis with an obstructing ureter stone. Until recently the pancreas and its duct system have been relatively inaccessible to the surgeon and, because of rapid autolysis of the gland at postmortem, poorly studied by the pathologist. There has been a large body of animal experimentation which can mimic the disease in man, but actually throws little light on its pathogenesis. Too many anatomic variables obtain and the methods to date have used pressures and artificial factors that cannot be translated to the human situation.

It was impressive throughout these injection studies that the terminal 4 to 8 millimeters of the major pancreatic duct (Wirsung) was intimately associated with the terminal common bile duct just proximal to the papilla of Vater. Because of its embryologic derivation from the common bile duct and its common efflux with the

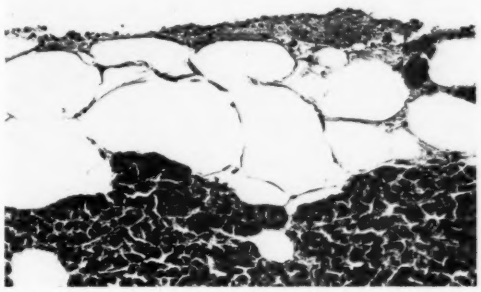

FIG. 21. Photomicrograph showing the adipose type pancreatic capsule in an obese adult. ×121.

common bile duct, one might almost consider the pancreatic duct or Wirsung as part of the extrahepatic biliary system and subject to the diseases of this system. Twenty years ago, Fallis and Plain had already made the observation that half of the cases of acute pancreatitis were found in patients with biliary tract disease. Again over 50 years ago Opie (17) had collected 31 cases of fatal pancreatitis associated with gallstones. In a recent extensive survey of pancreatitis by Berman, Dunn, and Straehley, 50 per cent of the 640 cases surveyed were associated with biliary tract disease and effective treatment of the biliary tract disease caused resolution of the pancreatitis in almost all cases.

It was striking to observe the increased incidence of sparse or atresic duct systems in this series in association with chronic cholecystitis and cholelithiasis, suggesting subclinical involvement of the pancreas by recurrent infection and obstruction. Here the specimens showed attrition of the duct system with irregular primary ducts, fewer and coarser collecting ducts, rare or absent terminal branching, and had the appearance of old, gnarled oak trees (Fig. 24). At first these same atresic specimens were correlated with aging alone, but on review of the data, the relationship was more direct with the incidence of gallstones (which increase in frequency with each decade of life) than with age alone. Of

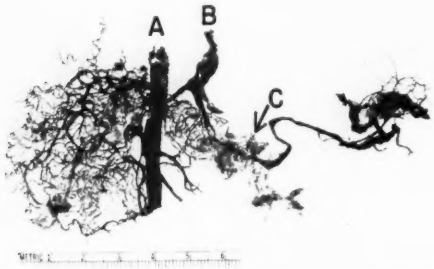

FIG. 22.

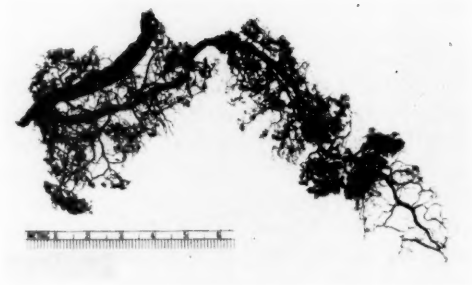

FIG. 23.

FIG. 22. Cast specimen in which the vascular and ductal systems were injected. *A* represents the superior mesenteric artery, *B* the celiac axis, and *C* is fine duct filling just proximal to the location of the carcinoma.

FIG. 23. Cast specimen which was injected through the common bile duct after first clamping the duodenal ampullary mucosa. The larger common duct is seen traversing the pancreatic substance to merge with the duct of Wirsung.

FIG. 24. Twisted gnarled cast specimen from a 68 year old man with stones in both the gallbladder and the common duct. Marked chronic cholecystitis was present.

FIG. 24.

interest was the observation that the aged without gallstones had rich duct patterns.

In many of the specimens, atresic areas were predominant only in segmental areas of the pancreatic tree, suggesting that there had been focal pancreatitis secondary to obstruction of collecting or terminal ductules, conceivably as a result of inspissated secretions (demonstrated in some of the histologic preparations) or to duct metaplasia (Fig. 17).

The presence of a lesser separate proximal papilla for Santorini in 33 per cent of the specimens indicates a possible "blow-off" mechanism, which may reduce the incidence of pancreatitis when the main Wirsung duct is obstructed. There are no data to indicate if the incidence of pancreatitis is higher in individuals without a Santorini outlet. The main pancreatic duct obstruction could well be relieved by a patent Santorini system when the two communicate.

Again, there was a striking incidence of bare or atresic specimens in the group of patients who were identified as alcoholics. The current theory of Dreiling and associates of the relationship of alcoholism to pancreatitis suggests that with a high oral alcohol intake there is increased volume of secretion of pancreatic juice via the secretin mechanism, against an obstruction produced by spasm and edema of the papilla secondary to alcoholic duodenitis. "Alcoholic" pancreatitis in the same survey by Berman and associates represented almost a third of the entire group and was unrelated to biliary tract disease.

The finding of rather consistent points of narrowing or sharp angulation of the main pancreatic duct (1) at the junction of the ducts of Wirsung and Santorini and (2) in the midbody may have clinical importance in the management of pancreatic duct obstruction. Thal, Goott, and Margulis recently reported 8 cases in which they demonstrated various sites of pancreatic duct obstruction in chronic pancreatitis. In Cases 6 and 7 there was a demonstrable stricture 4 centimeters from the papilla of Vater which could well represent the site of junction of Wirsung and San-

torini when there is both narrowing and angulation.

The absence of a true pancreatic capsule previously recognized has been observed in this study. In many specimens, the terminal ductules and acini were filled to the surface of the gland and leaked easily from the surface if too much pressure was applied during the injection. This finding may well account for injury to the pancreas at the time of surgery when even superficial ties of the so-called pancreatic capsule may injure terminal ductules and initiate gland digestion and pancreatitis.

In the light of the foregoing, it is suggested that in all cases of fatal pancreatitis studies be made, as outlined, of the duct system as well as of the parenchyma of the pancreas. Just as studies in cases of myocardial infarction are directed to the coronary vessels rather than to the heart muscle alone, so investigations of the pathogenesis of pancreatitis should be directed to the duct system of the pancreas.

SUMMARY AND CONCLUSIONS

1. A technique has been described to demonstrate the pancreatic duct system in man, using postmortem preparations.

2. The normal anatomic variants of the ducts of Wirsung and Santorini and their relationship to the common bile duct have been shown, as well as rather constant sites of narrowing and angulation of the main channel.

3. Variations in patterns of the main duct, collecting ducts, and ductules were noted in diseases which have clinically some relationship to pancreatitis.

4. Emphasis was placed on the role of ductal disease in the etiology of chronic pancreatitis.

5. This kind of study directed to cases of fatal hemorrhagic pancreatitis may well shed light on the role of ductal disease in its pathogenesis.

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OPERATIVE PANCREATOGRAPHY

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THERE IS AGREEMENT among physicians that a procedure resulting in opacification of the pancreatic ducts and their visibility by roentgenography would be of great diagnostic aid. A search is being made for a material which would be concentrated selectively by the pancreas, comparable to the oral cholecystographic examination, but as yet has not been rewarding. Visualization of the pancreatic duct system has been attempted at the time of a definitive biliary tract operation. Experiences with this technique have been helpful in the hands of a few and unrewarding, even dangerous, in the hands of others. Physicians who have had unsatisfactory experiences with operative pancreatography condemn it on the basis that subsequent to the visualization of the pancreatic ducts there may develop a severe pancreatitis which threatens the patient. Certainly, operative pancreatography, which is performed by way of a duodenotomy, direct intubation of the main pancreatic duct, and the forceful injection of radiopaque material, may be fraught with the danger of rupture of the ducts and the release of activated enzymes into the pancreatic parenchyma. Regardless of the relative merits of this direct visualization of the pancreas, there is no doubt that even a duodenotomy added to a specific biliary tract operation would carry with it a significant complication potential. An attempt has been made in this clinic to develop a simple method of visualizing the pancreatic ducts which does not add to the mortality or morbidity of the operation.

PROCEDURE

Figure 1 demonstrates the steps by which an operative cholangiogram and an operative pancreaticogram can be made during elective cholecystectomy without interfering with either the common bile duct or the duodenum. In Figure 1a is illustrated the technique of placing the gallbladder on tension and placing a silk mattress suture about the cystic duct after identifying its attachment to the common bile duct. This is electively done about 4 or 5 millimeters from the common bile duct itself. In Figure 1b, a grooved director is introduced through a small transverse incision proximal to the suture. It is inserted past the spiral valve of Heister, obliterating the obstructing folds of mucosa. A polyethylene catheter of a suitable caliber—a No. 18 to 20 French—is inserted over the grooved director well into the common bile duct. As shown in Figure 1c, the suture is now tightly tied down about the catheter. At this point, operative cholangiography is carried out in the customary fashion with the injection of 10 cubic centimeters of 50 per cent urokon® for visualization of the biliary duct system, including both hepatic ducts and the intrahepatic radicals as well as the distal common duct, and the determination of free flow into the duodenum. In order to obtain the pancreaticogram, this procedure is done in identically the same fashion with the instillation of the radiopaque medium as indicated preceded by about 10 seconds with the intravenous injection of 10 or 15 milligrams of morphine sulfate. Since these patients are intubated, the anesthetist can carry respirations on despite the respiratory depression of the morphine. By the pharmacologic response to the injected morphine sulfate, the sphincter of Oddi is closed and, if the main pancreatic duct communicates with the main bile duct at its distal end, there will be reflux of the radiopaque material into the pancreatic

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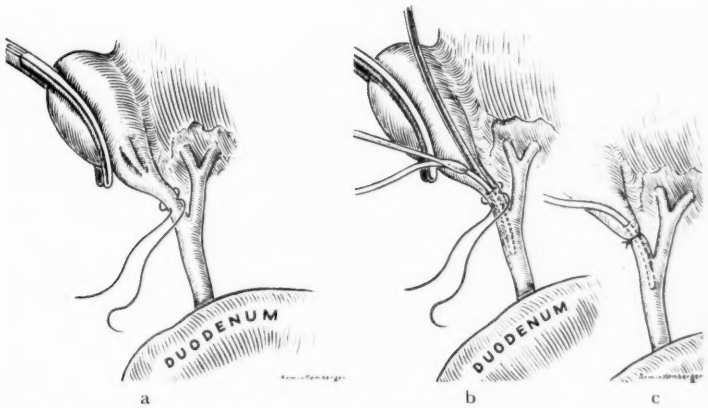

FIG. 1. Sketches made at the operating table illustrating the technique employed in operative pancreatography. a, The gallbladder is placed on tension and a silk mattress suture is placed about the cystic duct. b, Through a transverse incision in the cystic duct, a polyethylene catheter is passed over a grooved director. c, The suture is tied snugly over the catheter.

ducts. There is no danger of rupture of the intrapancreatic ducts, because if the pressure rises high enough it will overcome the response of the sphincter to the injected morphine.

RESULTS

The necessity for performing this examination arises rather infrequently. In the author's personal experience the procedure has been done only 18 times in the past 4 years. It is generally assumed that the indications for the operative procedure can be summarized as (1) recurrent attacks of pancreatitis, unexplained by clinical and/or laboratory diagnostic findings or (2) recurrent attacks of pancreatitis without demonstrable biliary tract disease.

The following briefly described cases will illustrate the typical findings in the 18 patients who have been subjected to this diagnostic procedure. Of the 18, results in 4 were completely unsatisfactory possibly because the main pancreatic duct did not communicate freely with the main common bile duct. Of the 14 remaining patients, 3 showed significant demonstrable disease as will be recounted by instances.

Figure 2 illustrates a normal case. Results of a preoperative cholecystographic examination were negative, but at the time of operation the gallbladder was found to contain two stones, and subsequent microscopic examination revealed chronic cholecystitis. Operative pancreatography was carried out as described and a normal pancreaticogram was found. In Figure 2, left, is a black and white opacification for comparison with the roentgenogram, right. In examinations repeated in other patients this represented the normal configuration.

Figure 3 represents an example of an unsatisfactory pancreaticogram performed through a T tube at the termination of an operative exploration of the common bile duct. A small stump of the pancreatic duct was visualized and it was assumed that this was the main pancreatic duct which provided drainage to a small segment of the head, presumably because an accessory pancreatic duct opening proximally into the duodenum had been retained developmentally as the major functioning duct of the pancreas itself. This was considered an unsatisfactory examination.

Figure 4 shows examination findings from a male patient, aged 42 years, who had had recurrent attacks of acute pancreatitis with-

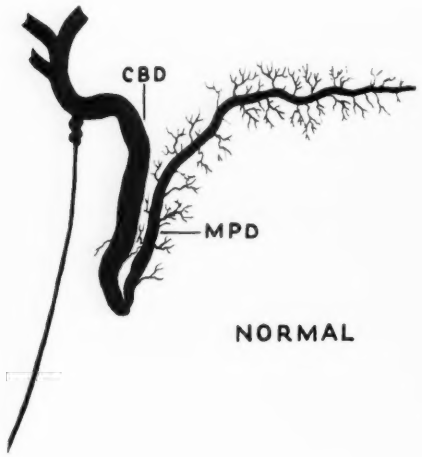

FIG. 2.

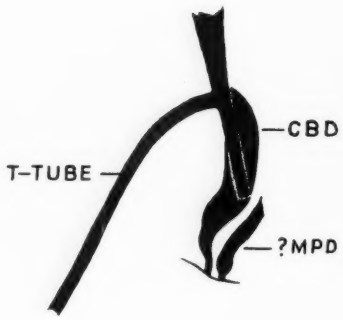

FIG. 3.

FIG. 2. Normal pancreaticogram. Left, Black and white opacification of the roentgenogram, right.
FIG. 3. Typical unsatisfactory visualization; presumably, the main pancreatic duct drains only a small portion of the head.

out demonstrable biliary tract disease. The patient was extremely obese and was not suitable for an extensive abdominal exploration. Operative cholangiogram revealed no abnormalities. The operative pancreaticogram, however, demonstrated sharp angulation of the main pancreatic duct cephalad, and there was opacification of the area immediately caudad to the distribution of the main pancreatic duct. Further exploration obtained by opening the gastrocolic omentum revealed a large pseudocyst which, because of the patient's obesity, was not found on the ordinary

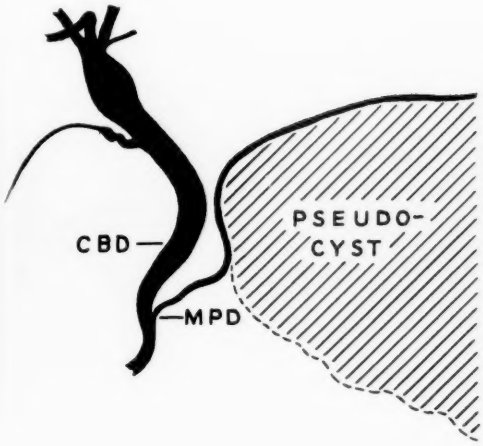

FIG. 4.

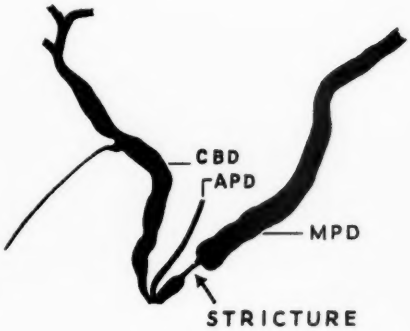

FIG. 5.

FIG. 4. Findings in a patient with a pseudocyst of the pancreas.
FIG. 5. Findings in a patient with a stricture of the main pancreatic duct.

exploratory procedure carried out during operation.

Figure 5 represents studies of a patient with recurrent attacks of unexplained pancreatitis without demonstrable biliary tract disease. At the time of operation there was chronic cholecystitis without stones. Operative pancreatography revealed a stricture of the main pancreatic duct with distal dilatation. An accessory pancreatic duct was seen, as indicated in the illustration. The patient was treated by duodenotomy and direct dilatation of this stricture and by placement of an indwelling polyethylene catheter

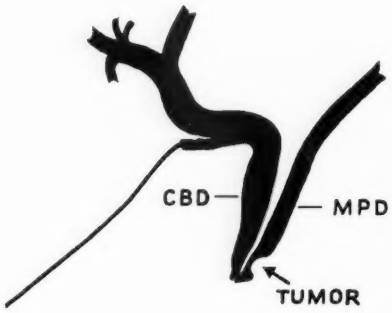

FIG. 6. Findings in a patient with an adenocarcinoma of the head of the pancreas obstructing the main duct.

brought out through the T tube in the common duct. This patient retained these catheters for 1 year and has been free of symptoms for 3 years since the removal of both the T tube and the indwelling polyethylene catheter.

Figure 6 represents an operative pancreaticogram performed on a patient with severe pancreatitis recurrent at very short intervals. On two occasions, 1 week apart, this patient came to the clinic with a serum amylase of 7,000 units and 11,000 units, respectively. No demonstrable biliary tract disease was apparent before operation or at the time of the operative procedure. Nevertheless, the gallbladder was removed. Operative cholangiography and operative pancreatography were carried out as described. A round, smooth filling defect was found in the main pancreatic duct with distal dilatation. Direct attack on this with excision and frozen section revealed it to be an adenocarcinoma of the head of the pancreas. A pancreaticoduodenectomy was performed, and the patient is living and well 48 months after the operative procedure. Parenthetically, it is important to point out that this patient is the only one who survived adenocarcinoma of the head of the pancreas among 93 such cases recorded in the Tumor Registry of the Yale-New Haven Medical Center.

SUMMARY

While it is very clear that the opportunities for which a surgeon would use this procedure are not frequent, nevertheless it is an additional diagnostic facility which he can use as required or indicated by his preoperative examination of the patient or his operative observations. Since it is performed only through the cystic duct, there is no additional morbidity or mortality associated with the diagnostic technique. Its use is advocated in puzzling cases of pancreatitis which recur very frequently, or in those in which no demonstrable biliary tract disease can be found and no medical cause, such as familial hypercholesterolemia, can be demonstrated. The fruitful uncovering of unrecognized pancreatic disease makes this technique one that should be considered in the complete operative examination of the patient. Since it is technically no more difficult than operative cholangiography, it probably should be coupled with such a diagnostic procedure whenever the pancreas has been implicated in the disease.

GASTRIC RETENTION DURING ORAL CHOLECYSTOGRAPHY DUE TO UNDERLYING LESIONS OF THE STOMACH AND DUODENUM

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UNLIKE the roentgenologic examination of the gastrointestinal tract into which the radiopaque material is introduced directly, satisfactory opacification of the gallbladder is dependent upon the absorption of the medium from the small intestine, its transportation through the portal circulation, and excretion by the liver into the biliary system. Faint or no visualization of the gallbladder, therefore, is not necessarily indicative of gallbladder disease, since impairment of gastric emptying, intestinal absorption, or hepatic function may interfere with satisfactory opacification.

The presence of orally administered radiopaque medium in the colon during cholecystography is not uncommon and is due, in part, to failure of complete intestinal absorption. This finding has no clinical significance. In contrast, the presence of residual material in the stomach represents gastric retention of at least 10 to 14 hours' duration and may therefore be indicative of partial or complete obstruction with altered gastric motility. In 1950, Gottlieb and Beranbaum reported a series of 7 patients in whom gastric residue was found during oral cholecystography; 5 of these patients had organic lesions of the stomach or duodenum. In 1955, Teplick and Adelman reported 5 similar studies in which a pathologic condition of the upper gastrointestinal tract was uncovered after the demonstration was made of retained gallbladder medium in the stomach.

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We have found a high incidence of organic disease of an obstructive nature in the stomach or duodenum of those patients in whom retention of orally administered medium during cholecystography was demonstrated. Because the significance of residual cholecystographic medium in the stomach is often not appreciated and therefore overlooked, a study was undertaken in this department to evaluate the importance of this roentgenologic finding.

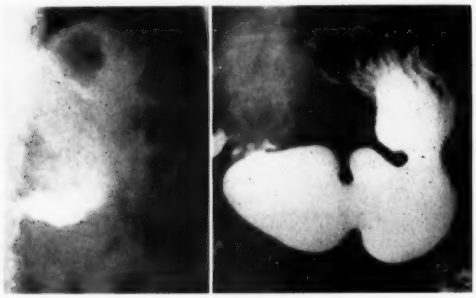
MATERIALS AND METHODS

The records and roentgenograms of 500 studies previously reported as poor or no visualization of the gallbladder after routine and reinforced oral cholecystography were reviewed. Those in which upper gastrointestinal residue was identified were further evaluated and followed up. Those patients who later were examined at operation or autopsy formed the basis of this report.

In addition, 1,000 consecutive cholecystograms carried out in this department during 1959 were reviewed for gastric retention of contrast media. Those in which this was found and the results of further investigation were included in this study.

RESULTS

Gastric retention was demonstrated as due to underlying lesions in 45 patients. Duodenal ulcer was diagnosed in 17, carcinoma of the stomach in 4, carcinoma of the pancreas in 2, intestinal obstruction in 2, extrinsic lymphadenopathy in 1, acute and chronic cholecystitis in 9, diabetes mellitus



a b

FIG. 1. Case 1. a, Retained oral contrast medium is seen in the stomach. b, A duodenal bulb deformity with ulceration may be identified on the barium study.

in 2, and renal disease in 2. In 6, diagnosis was unknown. Further roentgenologic studies were obtained. The diagnoses were confirmed at subsequent operation and/or autopsy in 31 of these patients.

Of the group of 500 patients who showed poor or no visualization of the gallbladder on initial studies, 33 or 6.6 per cent exhibited retention of contrast material. Of the group of 1,000 consecutive cholecystographic studies, 12 or 1.2 per cent showed evidence of gastric retention of the radiopaque medium. In the majority of these, a lesion associated with or affecting the patency or motility of the stomach or duodenum was demonstrated.

COMMENTS

In the normal patient, the more commonly used cholecystographic media are absorbed from the small intestine and may be demonstrated in the biliary system as early as 2 hours after ingestion. Absorption occurs only in an alkaline medium at *p*H 8 so that none occurs in the stomach. Optimum opacification of the gallbladder is present at about 10 to 12 hours. A small residue of the radiopaque material is not infrequently visualized in the proximal part of the colon at that time.

Impaired gastric motility with obstruction resulted in a delay in the passage of the contrast material into the small intestine. This was identified on the initial scout film of the abdomen in the form of gastric retention during cholecystography. Poor or no visualization of the gallbladder, therefore, was not definitive roentgenologic evidence of biliary disease. In those instances in which the emptying time of the stomach was delayed by the presence of an obstructing lesion, inflammatory change, or neuropathy, it is possible that insufficient contrast material was absorbed for concentration in the gallbladder.

A practical application of the roentgenologic demonstration of gastric retention may be illustrated in the following cases.

CASE 1. A 70 year old female with a recent episode of abdominal pain, nausea, and vomiting was admitted with a clinical diagnosis of acute cholecystitis. Oral cholecystography demonstrated nonopacification of the gallbladder with gastric retention of radiopaque material (Fig. 1). A barium study revealed a large duodenal ulcer which was subsequently removed by subtotal gastrectomy. Six weeks after surgery a normal gallbladder was demonstrated on oral cholecystography.

CASE 2. A 72 year old female with a history of right upper quadrant abdominal pain and weight loss demonstrated retention of telepaque in the stomach (Fig. 2). A gastrointestinal examination suggested a neoplasm in the antral portion of the stomach; this was confirmed at operation.

CASE 3. A 52 year old female with a history of chronic alcoholism, esophageal varices, and ascites was admitted with jaundice and right upper quadrant pain. The gallbladder failed to visualize on oral cholecystography, and contrast material was retained in the stomach (Fig. 3). A gastrointestinal study revealed atony of the stomach with decreased peristalsis. At subsequent operation, an acutely inflamed gallbladder with calculi in its lumen and in the common bile duct was demonstrated.

DISCUSSION

These studies suggested that the demonstration of retained gallbladder contrast medium in the stomach 10 to 14 hours after oral ingestion of the material was indicative of delayed gastric evacuation and partial or complete obstruction. In our experience, the underlying cause was frequently an organic lesion in the upper gastrointestinal tract which could be demonstrated by barium studies. In the majority of these, no intrinsic disease of the biliary system was present.

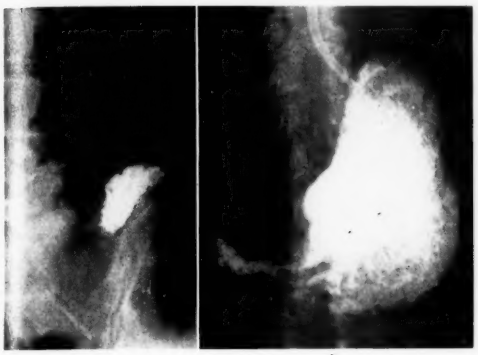


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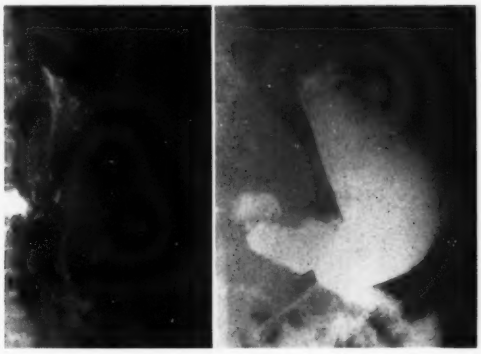
FIG. 2. Case 2. a, Gastric residue of food and contrast material is seen on the cholecystogram. b, A carcinoma of the pyloric antrum is demonstrated on the gastrointestinal study.



a b

FIG. 3. Case 3. a, Telepaque is dispersed in the stomach on the cholecystogram. b, A barium examination shows marked atony of the stomach with little evidence of peristaltic action.

The largest group in our series consisted of ulcerations, neoplasms, and other lesions which partially or completely impeded gastric emptying by obstructing the lumen or altering motility. The identification of such gastric residue proved to be a significant finding and suggested further investigation of the upper gastrointestinal tract, as in Case 1.

Extrinsic inflammatory involvement, particularly in the region of the gallbladder bed and the head of the pancreas, may readily disturb physiologic emptying of the stomach. Tapiovaara and Rala have described a number of instances in which adjacent inflammatory lesions, for example, acute cholecystitis, have impaired gastric emptying. This was particularly evident in our study in cases in which nonopacification of the gallbladder and gastric residue together with a normal barium examination of the stomach and duodenum usually indicated acute inflammatory disease of the gallbladder, as in Case 3.

Asymptomatic gastric retention as a manifestation of diabetic neuropathy has been described by Kassander. This phenomenon is often observed during a barium study of the gastrointestinal tract in severe diabetes. Marked decrease of peristaltic action, large amounts of gastric residue, and occasional bloating and gastric fullness are not uncommon findings.

Six patients in this series had normal gastrointestinal studies. At operation, the biliary system of each appeared normal. No satisfactory explanation for the gastric retention could be given.

We are aware that in the supine patient, ingested material tends to collect in the fundus of the stomach. In the sick patient, therefore, food does not readily leave the stomach unless the patient is placed on his right side or on his abdomen. In debilitated patients, improper positioning may result in anorexia, gastric fullness, regurgitation, altered gastric motility, and often a failure to obtain the expected effect of orally administered drugs.

The amount of retained radiopaque material varied. Minimal degrees of retention proved to be significant. No correlation could be made between the quantity of material retained and the underlying cause of the retention.

SUMMARY AND CONCLUSIONS

1. The retention of ingested gallbladder radiopaque material in the stomach after 10 to 14 hours was considered indicative of partial or complete obstruction or altered gastric motility. In our experience, the de-

layed gastric emptying was often due to an underlying obstructive lesion in the stomach or duodenum.

2. Although gastric residue during cholecystography was rare—1.2 per cent—its presence in those patients in whom unsatisfactory opacification of the gallbladder occurred was not an uncommon finding—6.6 per cent. The roentgenologist and surgeon should be aware of the possible significance of gastric retention during oral cholecystography.

3. An analysis is presented of the studies in 45 patients in whom gastric residue during cholecystography was demonstrated. The application of this roentgenologic finding to clinical situations involving gastroduodenal and biliary disease is discussed.

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MANAGEMENT OF URETERAL OBSTRUCTION PRODUCED BY RECURRENT CANCER OF THE RECTOSIGMOID COLON

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TEN MALE PATIENTS with carcinoma of the rectum or sigmoid colon have required nephrostomies for ureteral obstruction in the 4½ years from 1954 to 1959 at the Veterans Administration Hospital, New York. For the entire hospital, during the same period, a diagnosis of carcinoma of the rectum and sigmoid was established in 148 patients. Total admissions to the hospital during this time were 30,417.

This consequence of colonic carcinoma has received negligible attention by other surgeons. Although Spillane and co-workers studied 9 patients who presented the characteristic medial deviation of the ureters, their report did not express the ratio this number bore to the general occurrence of colonic carcinoma in the same hospital. Marshall and Schnittman have reported 3 patients in whom ureteral obstruction was produced by iliac lymphadenopathy and in whom metastatic carcinoma of the rectum or sigmoid was present; but, again, no comparison with a larger series was recorded. MacLean and Fowler reported 39 instances of secondary metastases of tumor to the ureter in 10,223 autopsies which were performed over a period of 22 years at a British Royal Victoria Hospital. Twenty-one of these 39 subjects had a lesion surrounding the ureter and occluding it. In these 21, the tumor was said to have originated in the rectum or sigmoid colon. Carcinoma of the rectum, in 1 additional autopsy, was found as an actual lesion in the ureter.

Relying on our measured incidence of this complication, surgeons may generally expect that ureteral obstruction requiring urinary diversion will develop in 7 of every 100 patients with carcinoma of the rectum or sigmoid. Earlier detection of this complication may permit a variety of urinary diversions less damaging to the kidney than the emergency nephrostomies which these patients required.

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CASE REPORTS

CASE 1. F. P., a 66 year old male, was admitted to the Veterans Administration Hospital, New York, on 21 October 1955 with abdominal distention. Abdominoperineal resection for carcinoma of the rectum had been performed in October 1953. The lesion had invaded the bladder at the junction of the left ureter, prostate, and bladder and had to be separated in the area by sharp dissection.

On admission, the patient's blood urea nitrogen was 59. Two days later the blood urea nitrogen was 150. At cystoscopy on 23 October 1955 the ureteral orifices could not be catheterized. Bilateral nephrostomy was performed the same day. Bilateral hydronephrosis was found at operation. The day after operation, urinary output from the left kidney was 1,300 cubic centimeters and from the right 1,400 cubic centimeters. Six days later the patient was eating, abdominal distention was gone, and the blood urea nitrogen was 39. Anterograde pyelograms, performed 1 month after nephrostomies, showed complete occlusion of the lower third of each ureter (Fig. 1).

The abdomen was explored on 6 December 1955. The lower thirds of both ureters were surrounded by tumor. Both ureters were divided above the obstruction. The defects between the divided ureters and the bladder were bridged with polyvinyl plastic prostheses. The patient deteriorated rapidly and died on 18 December 1955.

At autopsy, the lower part of both ureters, posterior bladder wall, and seminal vesicles were invaded by tumor. The kidneys showed acute pyelonephritis and papillary necrosis.

CASE 2. M. S., a 64 year old male, entered the Veterans Administration Hospital, New York, on 8 June 1956. An abdominoperineal resection for carcinoma of the rectum had been performed in March 1955. The operative report stated that the nodes posterior to the rectosigmoid were involved. In Febru-

FIG. 1. Case 1. An anterograde pyelogram performed 1 month after bilateral nephrostomies. The characteristic medial deviation of the ureters may be observed. Complete ureteral obstruction is apparent.

ary 1956 the patient became anuric and comatose. Left nephrostomy was performed in another hospital.

Cystoscopy performed at the Veterans Administration Hospital on 13 June 1956 disclosed that the bladder was invaded by tumor. Ureteral catheters could be passed only a few centimeters on both sides. The left nephrostomy was revised 6 days after admission. A right nephrostomy was performed 15 days after admission. The patient died 4½ months after admission.

Autopsy showed bilateral chronic pyelonephritis and gross infiltration of both ureters by tumor.

CASE 3. L. W. was admitted to the Veterans Administration Hospital, New York, on 26 November 1956 with anorexia of 5 days' duration. Abdominoperineal resection of the rectum for carcinoma had been performed on 26 January 1953. The operating surgeon wrote: ". . . The mass was densely adherent to the posterior surface of the bladder and had probably invaded at this point. . . . The pathologic specimen revealed metastases to two of the pericolic lymph glands." Three years after the initial operation a permanent cystotomy had been performed.

After admission, the patient's urinary output fell sharply, and the blood urea nitrogen rose from 65 to 195. Cystoscopy through the suprapubic sinus disclosed extensive invasion of the bladder by tumor. Bilateral nephrostomy was performed on 12 December 1956. Left hydronephrosis and right pyonephrosis were found.

The patient improved for 2 weeks. Urinary output increased to 3 liters daily, and the blood urea nitrogen fell to 93. Urinary output declined, the blood urea nitrogen rose to 198, and the patient died on 7 January 1957. No autopsy was permitted.

CASE 4. M. M., a 36 year old male, was admitted to the Veterans Administration Hospital, New York, on 18 January 1957 with persistent right flank pain of 2 months' duration. Although the patient had had diarrhea for many years, previous proctoscopy and barium enema of the colon had been reported on several occasions as disclosing no disease.

By intravenous pyelogram there was no visible function of the right kidney. The left pyelogram was of normal appearance. Cystoscopy disclosed a normal bladder, but a catheter could not be passed more than 7 centimeters up the right ureter. Despite an ostensibly normal and unobstructed left kidney, the blood urea nitrogen rose from 38 to 64 during the first 12 days of hospitalization.

Without a definite diagnosis, right nephrostomy was performed. Dilatation of the right renal pelvis and ureter was found. Re-examination of the rectum disclosed a friable irregular mass above the prostate. Several attempts to pass a proctoscope to this region were unsuccessful. Neither a barium enema nor a gastrointestinal series revealed an intrinsic lesion of the alimentary system.

Despite nephrostomy, the blood urea nitrogen continued to rise. Repeat cystoscopy, 2 weeks after the right nephrostomy, disclosed a partial obstruction of the left ureter 10 centimeters above the bladder and residual urine of 60 cubic centimeters in the left renal pelvis. A left nephrostomy was performed. At the time of this second operation, the peritoneal cavity was manually explored through a small incision in the peritoneum. Many hard, matted masses could be palpated in the region of the rectosigmoid colon. A biopsy of this tissue revealed an adenocarcinoma with many mucin-containing cells and acini.

On the fourth day after the second nephrostomy the blood urea nitrogen had fallen to 30. After brief improvement, the patient gradually declined and died on 11 September 1957. No autopsy could be obtained.

CASE 5. N. B., a 70 year old male, was admitted to the Veterans Administration Hospital, New York, on 10 July 1957 with low back pain. Abdominoperineal resection for carcinoma of the rectum had been performed in January 1957. The operating surgeon found no extension of the tumor beyond the bowel.

Intravenous and retrograde pyelograms demonstrated filling defects of the right renal pelvis. On 3

September 1957, a right transabdominal nephrectomy was performed. Tumor nodules, presumably from the rectal carcinoma, were found in the liver. The pathologist reported papilloma of the renal pelvis. In spite of its size and widespread character, the tumor showed no histologic evidence of malignancy.

Prostatic obstruction necessitated an indwelling urethral catheter. Transurethral resection of the prostate was performed on 30 September 1957. The pathologist reported a carcinoma of the prostate; the primary site was undetermined. The tumor, however, was glandular and unlike that in the renal pelvis. Blood urea nitrogen on 21 October was 75. Catheterization of the left kidney disclosed 150 cubic centimeters of residual urine. Retrograde pyelograms showed a dilated ureter with constriction a few centimeters above the bladder (Fig. 2). Left nephrostomy was performed the same day. Three weeks later, the blood urea nitrogen had fallen to 22. The patient improved for a few months, then became anorectic, and died on 23 January 1958.

At autopsy, the prostate and seminal vesicles were found to be replaced by a large tumor mass. Carcinoma invaded the bony pelvis and retroperitoneal area. The left ureter, traced to the left lateral wall of the bony pelvis, ended in the tumor mass.

CASE 6. J. R., a 62 year old male, entered the Veterans Administration Hospital, New York, on 26 August 1957 with abdominal cramps, weight loss, anorexia, and vomiting. An abdominoperineal resection had been performed for a rectal carcinoma. The pathologist said that the tumor was confined to the bowel wall.

The patient's blood urea nitrogen on admission was 242. At cystoscopy, no tumor was seen in the bladder. A ureteral catheter could not be passed on the left. A ureteral catheter was passed to the right renal pelvis, which contained 2 ounces of cloudy residual urine. Pyelograms showed a dilated pelvis and ureter with abrupt stenosis 5 centimeters from the bladder (Fig. 3).

Bilateral nephrostomy was performed the same day. At operation, bilateral hydronephrosis was found. One month after nephrostomies, the blood urea nitrogen had fallen to 28. Improvement continued for 5 months. The patient died on 2 March 1958.

At autopsy, the liver, lungs, and bony pelvis contained tumor. Both terminal ureters were infiltrated and surrounded by tumor. Bilateral pyelonephritis was present.

CASE 7. J. L., a 46 year old male, was admitted to the Veterans Administration Hospital, New York, on 9 December 1957 with complaints of anorexia, weight loss, and urinary frequency. An abdominoperineal resection for carcinoma of the rectum had been performed in February 1957. The operative report stated that the bladder had been invaded by tumor.

On admission, the patient's blood urea nitrogen was 62. At cystoscopy, on 20 December 1957, no tumor was seen in the bladder. No ureteral catheter could be passed on the right. On the left, a catheter was passed with resistance to the renal pelvis, which contained 60 cubic centimeters of clear residual urine. A retrograde pyelogram showed a dilated left pelvis. Despite daily urinary output of about 1 liter, the blood urea nitrogen gradually rose to 165.

FIG. 2. Case 5. A retrograde pyelogram taken 8 months after abdominoperineal resection. The pelvis contained 5 ounces of residual urine. This is a drainage film, and the sharp obstruction is clearly shown. The opposite kidney had been removed because of a pelvic papilloma.

Two weeks after admission, bilateral nephrostomies were performed. At operation, matted lymph nodes were palpated retroperitoneally at the junction of the middle and lower thirds of the left ureter. For 5 days after operation, the blood urea nitrogen continued to rise and then, from a maximum of 210, declined to 107. The patient died on 27 January 1958. Permission for autopsy was not granted.

CASE 8. A. S., a 63 year old male, entered the Veterans Administration Hospital, New York, on 2 May 1958 complaining of scant urination for 5 days. An abdominoperineal resection of the rectum for car-

TABLE I.—SUMMARY

Patient Case No.	*Primary operation*	*Initial extension*		*Period of survival*		*Autopsy findings*
		Bladder	*Lymph nodes*	*Resection*	*Nephrostomy*	
F.P. 1	Abdominoperineal	Invaded	Involved	26 mos.	8 weeks	Pyelonephritis, widespread tumor
M.S. 2	Abdominoperineal	Not invaded	Involved	15 mos.	8 mos.	Pyelonephritis, widespread tumor
L.W. 3	Abdominoperineal	Adherent	Involved	48 mos.	26 days	None performed
M.M. 4	No operation	—	—	—	7 mos.	None performed
N.B. 5	Abdominoperineal	Not invaded	Not involved	12 mos.	3 mos.	Widespread tumor
J.R. 6	Abdominoperineal	Not invaded	Not involved	26 mos.	6 mos.	Pyelonephritis, widespread tumor
J.L. 7	Abdominoperineal	Adherent	Not described	11 mos.	24 days	None performed
A.S. 8	Abdominoperineal	Tumor peeled off	Involved	5 mos.	1 mo.	Pyelonephritis, cortical abscesses, widespread tumor
A.G. 9	Abdominoperineal	Tumor peeled off prostate capsule	Involved	9 mos.	9 days	Pyelonephritis, widespread tumor
P.C. 10	Abdominoperineal	Tumor peeled off	Not involved	—	—	

cinoma had been performed in January 1958. According to the surgeon who operated, tumor implants were found in the cul-de-sac and on the peritoneum over the bladder. Lymph nodes containing tumor were removed.

On admission, the patient had a blood urea nitrogen of 261. At cystoscopy, the bladder appeared to be infiltrated with tumor. A biopsy specimen was reported as carcinoma. Catheters could be passed only a few centimeters up each ureter. Retrograde pyelograms demonstrated dilatation and ureteral obstruction (Fig. 4). On the same day, bilateral nephrostomy was performed. Both renal pelves were dilated.

After nephrostomies, the blood urea nitrogen slowly fell but was still 73 at 14 days after operation. The patient died on 6 June 1958.

Autopsy showed carcinoma in the bony pelvis and liver. Both kidneys showed severe pyelonephritis and multiple cortical abscesses.

CASE 9. A. G., a 27 year old male, was admitted to the Veterans Administration Hospital, New York, on 1 August 1958 with nausea, vomiting, and weight loss. In November 1957 abdominoperineal resection of the rectum for carcinoma had been performed. At operation, the tumor mass was adherent to the prostatic capsule. Tumor-bearing nodes were found in the specimen.

On admission, the patient's blood urea nitrogen was 132. Cystoscopy was performed on 8 August 1958. A catheter was passed to the left kidney. Sixty cubic centimeters of clear urine were obtained. On the right side, an obstruction was met 6 centimeters from the bladder. Retrograde study revealed bilateral hydronephrosis.

A right nephrostomy and cystostomy were performed on 12 August 1958. A teflon ureteral substitute was inserted from the renal pelvis to the bladder. Although the blood urea nitrogen dropped to 50 by 16 August, the patient deteriorated and died on 21 August 1959.

At autopsy, recurrent tumor surrounded the lower ureters.

CASE 10. P. C., a 68 year old male, was admitted to the Veterans Administration Hospital, New York on 11 March 1959 with abdominal pain. An abdominoperineal resection of the rectum for carcinoma had been performed in June 1956.

The patient's blood urea nitrogen on admission was 114. A Foley catheter was inserted for urinary retention. In 5 days the blood urea nitrogen dropped to 58. At cystoscopy on 20 March, a ureteral catheter was passed to the right kidney. Hydronephrosis was found. A left ureteral catheter could not be passed. On ureteral and bladder drainage, the blood urea nitrogen dropped to 28. On 30 March, bilateral nephrostomy was performed. Left hydronephrosis was present. The blood urea nitrogen dropped to 17 within 2 weeks. This patient is living but remains in the hospital at the present writing.

COMMENT

Salient facts of the 10 patients are summarized in Table I. It can be seen that this was not a favorable series. Five of the patients had positive lymph nodes at the time of the original resection. Six of the patients

FIG. 3. Case 6. A retrograde pyelogram taken 22 months after abdominoperineal resection. No catheter could be passed on the left. The right renal pelvis contained 2 ounces of residual urine. The site of obstruction is clearly demonstrated.

FIG. 4. Case 8. An attempted retrograde pyelogram performed 5 months after abdominoperineal resection. Catheters could be passed only a few centimeters up either ureter. Medial deviation, the stigma of ureteral involvement, is clearly shown.

had some involvement of the bladder at the time of original resection; 4 of these had nodal involvement. Only 2 of the 10 patients were actually curable. The remaining 8 patients would generally receive a poor prognosis.

Analysis of the series presents two problems: (1) whether salvage would have been improved in this series if the original resection had been more radical, and (2) what measures can be used to prolong life in those patients for whom conservative operation was clearly the proper choice.

Brunschwig believes that exenterative surgery has some merit—particularly in male patients—when the primary growth is in the lower part of the colon. If one assumes that the patients would have survived the operation, one may be justified in concluding that pelvic exenteration would have salvaged some of the patients in this series. A curative operation requires excision of contiguous structures. A tumor cannot be "peeled off" with an expectation of cure.

The 7 patients in this series who showed involvement of the bladder or nodes died of tumor and ureteral obstruction. Excision of the rectum, bladder, and prostate—with diversion to an ileal conduit—might have prevented some of these deaths. We think that this series lends some support to the contention of Dockerty: "Perhaps 25 per cent of patients who have such inoperable adherent growths can be saved by courageous surgeons who recognize the possibility of encompassing all the malignant tissue by employing the principle of 'multiple organ resection'." Furthermore, results in

this series of 10 patients were inferior to the results published by Brunschwig in an almost identical series of 7 male patients who were subjected to pelvic exenteration.

The answer to the second problem is less controversial. Every patient with carcinoma of the lower part of the colon should receive the benefit of regular urinary tract appraisal. The exercise of a high degree of suspicion, the elicitation of complaints suggestive of azotemia, and the regular use of an interval intravenous pyelogram will spare some patients the necessity for what was provided the patients in this series, namely, emergency nephrostomies for patients *in extremis*. None of the patients in this series had had an interval intravenous pyelogram. If the surgeon who finds tumor invading or adherent to the bladder elects to perform routine conservative resection, he should caution the patient or the patient's physician to continue such urologic study.

Every patient in this series had extensive tumor at the time of death. But death in no case could be attributed exclusively to tumor. Death occurred when it did because of additional renal damage. This damage can be ascribed to two injuries: (1) prenephrostomy obstruction, and (2) the almost inevitable parenchymal damage that is caused by a nephrostomy and prolonged catheter drainage.

Detection of obstruction and incipient renal injury will permit performance of a superior form of diversion. While the patient's condition will stand such an operation, diversion of the urinary stream to an ileal conduit may be accomplished. Bricker's careful work and the experience of many surgeons have shown this technique to be best for renal preservation. It is the duty of the surgeon to suspect and detect such ureteral obstruction early enough to make Bricker's procedure feasible. When the urologist is confronted with dangerously uremic patients, he has no choice but to elect the easy technique of nephrostomy: easy for the surgeon, and perhaps immediately best for the patient, but bad, in the long run—as these deaths demonstrate—for the human kidney.

SUMMARY AND CONCLUSIONS

Ten male patients who required nephrostomies because of ureteral obstruction secondary to carcinoma of the distal large bowel are reported. This series lends some support to the utilization of pelvic exenteration as a treatment for carcinoma of the distal large bowel which has invaded contiguous organs. More positively, the cases reported confirm the intrinsic damage that results from nephrostomy. It is recommended that every patient who has carcinoma of the distal large bowel receive the benefit of interval urologic investigation. Early detection of ureteral obstruction will permit diversion to an ileal conduit—a technique that restores rather than damages the kidneys. Indifference to this not uncommon complication leads to obstruction, azotemia, and emergency nephrostomies—not, we believe, the best solution to a difficult problem.

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EFFECTS OF STORAGE ON ENZYME ACTIVITY AND VIABILITY OF SKIN

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THE TESTING of the viability of banked skin prior to its use and the evaluation and improvement of methods of skin preservation now require biologic tests such as autografting, tissue culture, and measurement of oxygen utilization. Previous work from this laboratory suggested that there is a close correlation of viability and the activity of an enzyme complex—succinic dehydrogenase—in banked skin (2) and skin injured by heat (1). Succinic dehydrogenase activity (SDA) is now measured quantitatively by a new colorimetric method, described previously (3), with tetrazolium dyes, which is rapid and convenient.

In these experiments stored guinea pig skin was autografted back on its donor and the viability or "take" of the grafts is correlated with measurements of the SDA. The data suggest a threshold level of SDA when guinea pig skin is viable. When the SDA is less than this level the stored skin was unlikely to survive when grafted back to its donor. Autografts were used to confirm whether or not the skin was viable.

The measurement of SDA is rapid and convenient and may be a satisfactory screening test for various modifications of techniques of skin banking.

MATERIALS AND METHODS

Albino male guinea pigs which weighed 400 to 450 grams were caged individually, fed a standard diet, and given water ad libitum. The animals were anesthetized by an intraperitoneal injection of sodium nembutal. The hair of the abdomen was clipped short and the remaining hair was removed with several applications of a depilatory cream.[1] After this was washed off, the skin surface was sponged with 70 per cent ethyl alcohol. Sterile technique was used for cutting, weighing, and storing the skin. Razor blades were used to cut the skin in order to minimize trauma, and care was taken to dissect the underlying areolar tissue and panniculus from the dermis. Full thickness skin was used in all experiments. Twenty-eight samples of skin were removed from the abdomen of each animal, and the defect was closed with silk sutures. Each sample of skin was weighed on a gram-atic balance as soon as it was removed; and then, to prevent drying, it was placed in a drop of saline in a labeled petri dish. The samples of skin were divided into 4 groups with 7 samples in each group. One group was used as a normal control, and the other 3 groups were stored for various intervals.

The method of storage was chosen arbitrarily. The pieces of skin were placed in sterile glass bottles with the dermis in contact with gauze which had been moistened with a nutrient medium. The medium consisted of Krebs-Ringer phosphate solution plus guinea pig serum (50 per cent), glucose (0.2 M), and streptomycin (500 units per c.c.). Since the pieces of skin were weighed prior to storage, they were arranged so that each piece subsequently could be identified with its prestorage weight. The bottles were sealed with screw caps and stored at 4 degrees C. for from 3 days to 2 weeks.

[1]Calcium thioglycollate.

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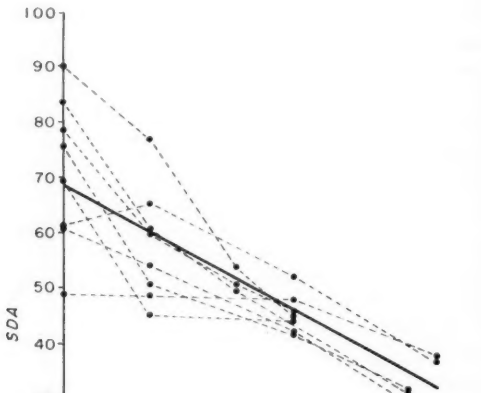

FIG. 1. Effect of storage on the SDA activity of skin. Data from Table I. The ordinate is the SDA in OD units per milligram of skin. The abscissa is the number of days stored.

Each group of 7 pieces of skin was tested for viability in the same manner. One piece (approximately 14 by 20 mm.) was placed on the back of the donor animal as a graft, and the remaining 6 pieces (each approximately 4 by 12 mm.) were tested for SDA by our quantitative method.

The piece of skin to be grafted was reversed to change the direction of hair growth in order to facilitate identification of the graft at a later date. It was then fitted into a defect created on the pig's back by removing an area of skin similar in size and shape to the graft. A small dry gauze dressing was applied and glued at the edges to the surrounding hair and skin. This protected the graft for 3 days and then was removed. The graft was considered to be viable if hair grew from it. The success or failure of the graft was always obvious and results were tabulated as "take" or failure.

SDA was measured by incubating the remaining 6 pieces of skin with tetrazolium. The enzyme transfers the hydrogen from the sodium succinate substrate to tetrazolium. Tetrazolium is reduced to formazan and is deposited in the skin as a water insoluble red pigment which is extracted and measured. The medium in which the skin was incubated was a modified Krebs solution containing 2,3,5-triphenyl tetrazolium chloride (.2 per cent) and sodium succinate (.5 per cent). The latter was added to insure the presence of an excess of substrate for the enzyme. Since the reaction between this enzyme and its substrate is more rapid and more reproducible under anaerobic conditions, the skin was incubated at the bottom of 3 cubic centimeter test tubes that were filled with the tetrazolium solution. The tubes were not stirred or aerated. After 2 hours of incubation in a water bath at 37 degrees C., each sample was removed, carefully blotted on filter paper, and placed in a test tube containing 1 cubic centimeter of methyl cellosolve. This was allowed to stand overnight. The extracted formazan colors the solution orange. The optical density (OD) of this solution was measured at 490 microns with the Beckman model DU spectrophotometer. The SDA is expressed in terms of OD units of formazan produced per milligram of skin.

RESULTS

The SDA of the control and stored guinea pig skin is shown in Table I. It is noteworthy that the reproducibility of the measurement is excellent. The SDA of 6 samples from the same animal show only small deviations from the mean; the standard deviation is practically always less than 5. Comparison of the mean SDA of unstored skin from animals shows more variability.

The SDA slowly declines under the conditions of storage used in these experiments. The data are listed in Table I and shown graphically in Figure 1. The effect of storage is quite uniform for any group of 6 samples from the same animal. Furthermore, although the initial SDA before storage varies considerably within the group, after storage

for 6 to 8 days, the mean SDA of the groups of 8 animals are very similar. In Figure 1, the broken lines connect the points for each individual animal. The lines converge after storage for 6 days. The solid line is the regression line calculated from the data and shows that with each day of storage the average decrease of SDA is 2.82 units ($P<0.001$).

The 32 skin samples were autografted to their donor animal after varying periods of storage. For all grafts the result was a clear cut "take" or "no take."

The ability of 32 skin grafts to take was correlated with the amount of SDA in the skin. When the SDA was equal to or greater than 50 OD units per milligram of skin, all grafts survived; when below that figure, less than half of the grafts survived. This is illustrated in Figure 2. Figure 3 is a photograph of one of the animals 3 months after grafting and shows the results of 4 skin grafts. The graft which had been stored 13 days did not take.

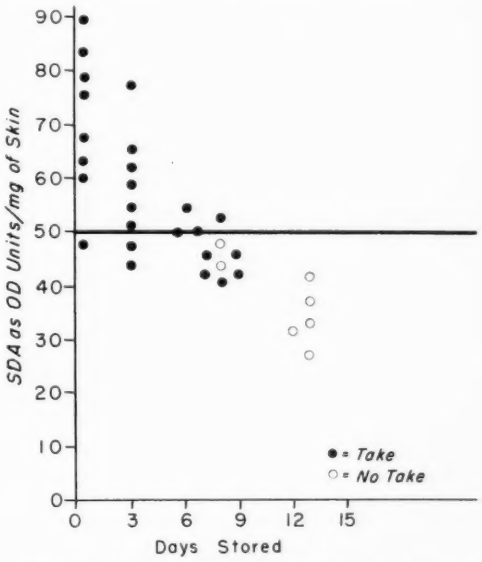

FIG. 2. Viability and SDA of stored skin. Ordinate is the SDA expressed as OD units per milligram of skin. Abscissa is the number of days of storage. Black dots are viable grafts, i.e., "takes"; open circles show enzyme activity of grafts which did not take.

DISCUSSION

It had been previously reported that frozen and dried skin loses all SDA and is nonviable. Also semiquantitative tests show that human skin stored at 2 degrees C. in moist saline gauze gradually loses its SDA in about 2 to 3 weeks. Most surgeons agree that viability of human grafts stored by this method is lost about this time. The method of storage used in the present experiments maintained viability of the guinea pig skin for only 10 days.

One of the earliest uses of tetrazolium salts was to test the viability of germinating seeds, and the present experiments suggest a correlation with the viability of stored skin. Most surgeons agree that viable homografts are better biologic dressings for the severely burned patient than nonviable grafts. The quantitative method now reported has obvious advantages for scientific work and will permit more precise and more rapid comparison of various methods of skin storage.

The testing of the viability of banked skin prior to its use and the evaluation and improvement of methods of skin preservation now require biologic tests such as autografting, tissue culture, and measurement of oxygen utilization. These have certain limitations. Skin grafting techniques require a considerable amount of time, the result must be observed for many days, and quantitative data require the use of large numbers of animals and human volunteers. The tissue culture method is an exacting qualita-

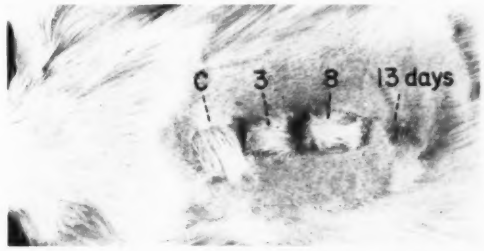

FIG. 3. Back of guinea pig 3 months after grafting. From left to right are represented the control graft and the grafts which were stored for 3, 8, and 13 days. The first 3 grafts survived. The fourth was lost and only a scar remains at the graft site.

TABLE I.—SDA OF STORED GUINEA PIG SKIN

Days stored	*Guinea pigs*	*No. of samples*	*Mean of samples**	*Standard deviation*	*Mean of group*	*Standard deviation*	*P*
	A	6	90.0	2.7			
	B	6	78.6	2.3			
	C	6	83.6	7.2			
0	D	6	75.6	1.3			
	E	6	61.1	5.0			
	F	6	60.8	5.7			
	G	6	49.0	4.4			
	H	6	69.4	4.3	71.0	13.6	.005
	A	6	76.9	4.6			
	B	6	59.8	1.7			
	C	6	60.8	8.3			
3	D	6	50.7	4.0			
	E	6	54.0	4.0			
	F	6	65.2	4.4			
	G	6	48.8	4.4			
	H	6	45.1	3.9	57.7	10.3	.001
	A	6	53.6	3.3			
6	B	6	50.5	4.1			
	C	6	49.3	5.3	51.13	2.22	.005
	A	6	44.7	3.0			
	B	6	45.9	4.1			
	C	6	43.8	2.1			
8	D	6	41.5	4.5			
	E	6	41.9	4.6			
	F	6	51.9	9.2			
	G	6	47.7	3.1			
	H	6	43.8	2.7	45.15	3.39	.001
12	D	6	31.4	1.2			
	E	6	25.9	4.6			
	F	6	36.5	3.5			
13	G	6	37.4	2.7			
	H	6	40.9	2.1	35.18	6.47	.025

*SDA is expressed as OD units per mgm. of skin.

tive test of viability but again requires considerable time, more equipment, and sterile technique. The grafting of skin to the chorioallantoic membrane of the chick embryo may be useful but has similar disadvantages. Oxygen uptake measurements are an additional test of viability but we encountered a problem of bacterial growth when measuring the respiration of skin that had been stored more than 3 days.

The *sine qua non* of viability will always be the survival of the graft on the donor. In contrast to this and other established methods for testing viability, the measurement of SDA requires only a few hours, sterile technique is unnecessary, and the test can be done with equipment which may be found in almost any biochemical laboratory. Further experiments are needed to determine the effect of storage on the SDA of human skin and the relationship of the activity of this enzyme to its viability.

Measurement of SDA may be a rapid and convenient method to test the viability of banked skin prior to its use on a patient. It may also be a useful method to compare rapidly various methods of freezing, various media, temperatures, and other conditions for skin storage.

SUMMARY AND CONCLUSIONS

1. Data are presented on the succinic dehydrogenase activity (SDA) of 144 samples of skin from 16 guinea pigs before and after storage at intervals up to 13 days. Thirty-two samples stored under the same conditions were grafted back to the donor animal.

2. The SDA of guinea pig skin which has been stored at 4 degrees C. in a nutrient medium decreases 2.82 units per day.

3. When the SDA of guinea pig skin stored under these conditions is less than 50 OD units per milligram it is unlikely that the autografts of this skin will survive.

4. The measurement of the SDA in stored guinea pig autografts appears to be a satisfactory, rapid, and convenient method of testing the viability.

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A PATHOLOGIC STUDY IN 55 AUTOPSIES AFTER RADICAL SURGERY FOR CANCER OF THE CERVIX

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RADICAL or superradical surgery for cancer of the cervix has an established place in the control of some cases that would otherwise be untreatable. The benefits to certain cancer patients have been reported by Brunschwig, Meigs, Parsons, and others. The shortcomings or failures of these techniques have also been noted, but no detailed analysis of the findings in patients dying after radical pelvic surgical therapy for cancer of the cervix has appeared. A sufficient number of cases in which autopsy was performed has now been collected to warrant such a report.

MATERIAL AND METHODS

In this study all available pathologic material has been reviewed from unselected instances of cancer of the cervix in which autopsy was performed at some time after radical pelvic surgery. Material was drawn from the Massachusetts Memorial Hospitals, the Lemuel Shattuck Hospital, the Pondville Hospital, and the New England Deaconess Hospital, and included cases in which a Wertheim hysterectomy, with or without an associated pelvic lymphadenectomy, or an anterior or total exenteration operation had been performed. Two cases also were reviewed through the courtesy of pathologists at the Boston City Hospital.

A total of 411 cases of cancer of the cervix was found in which these surgical procedures were performed. In 55 of this number, autopsy was performed at varying intervals after the definitive surgical procedure.

Autopsy records were reviewed to find the immediate cause of death, the major gross pathologic changes, and the presence of residual tumor and its location. All of the microscopic slides from both surgical and autopsy material were reviewed, particularly as to the presence or absence of lymphatic and blood vessel invasion, lymph node involvement, and irradiation effect in the operative specimens. A few of the cases were studied by means of giant histologic sections. Clinical records were also reviewed, particularly with regard to the preoperative evaluation of the extent of disease, the findings at operation, and the type of the procedure performed.

The 55 patients ranged from 28 to 72 years of age at the time of diagnosis, with approximately three-fourths of them between the ages of 40 and 60 years. Three patients had undergone previous surgical treatment for cervical cancer, and 31 had had irradiation therapy at some time before the definitive surgical procedure was performed. The type and amount of therapy given to these 31 patients varied widely, however; and in many instances was considered to be inadequate.

SURGICAL PROCEDURES PERFORMED

Definitive surgical therapeutic procedures fell into 4 categories; (1) Wertheim hysterectomy without node dissection—3 cases; (2) Wertheim hysterectomy with bilateral pelvic lymphadenectomy, as performed by Meigs—15 cases; (3) anterior exenteration, consisting of Wertheim hysterectomy with

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TABLE I.—CORRELATION OF CLINICAL AND PATHOLOGIC ASSESSMENTS OF EXTENT OF CANCER WITH TYPE OF DEFINITIVE SURGICAL THERAPY

	No. of cases	*Vagina*	*Uterus*	*Para-metrium*	*Bladder*	*Rectum*	*Iliac and obturator nodes*	*Blood vessel invasion*	*Lymphatic invasion*
EPIDERMOID CARCINOMA OF THE CERVIX									
STAGE I									
Wertheim	7	1	5	1	—	—	0	3	4
Anterior exenteration	1	1	0	0	1	—	0	1	1
Total	8	2	5	1	1	—	0	4	5
STAGE II									
Wertheim	11*	5	4	5	—	—	5	4	4
Anterior exenteration	3	3	3	2	2	—	1	1	3
Total exenteration	4*	3	1	2	3	2	0	2	2
Total	18	11	8	9	5	2	6	7	9
STAGE III									
Anterior exenteration	3	3	1	1	1	—	1	2	2
Total exenteration	11	11	6	6	6	6	5	5	6
Total	14	14	7	7	7	6	6	7	8
STAGE IV									
Total exenteration	15	13	8	7	10	7	6	4	7

*One case in which no tumor was found in operative specimen but was present in previous biopsy specimen.

bilateral pelvic lymphadenectomy, total cystectomy, and vaginectomy—7 cases; and (4) total pelvic exenteration, including a Wertheim hysterectomy with bilateral pelvic lymphadenectomy, total cystectomy, abdominoperineal resection of the rectosigmoid and anus, and resection of the vagina and vulva—30 cases. In all of the anterior and total exenteration operations reported here, the ureters were transplanted to the colon. In the total exenteration group these patients were left with "wet" colostomies.

From a review of the operative notes, it would appear that although preoperatively the surgeon thought a curative operation could be performed in each of the cases, during the course of the procedure it became apparent in some 15 cases that the operation would be at best only a palliative one. In most of these cases the surgeon believed that some tumor had been left behind.

SURGICAL PATHOLOGY

As noted before, epidermoid carcinomas of the cervix predominated in all age groups, with 28 grade II and 20 grade III tumors found. There were in addition 1 grade I epidermoid carcinoma of the cervix, 5 adenocarcinomas, and 1 adenoacanthoma of the endocervix.

In 2 cases, no tumor was found in the specimen from the definitive operative procedure. In 1 of them, a case in which a Wertheim hysterectomy was performed, no tumor was found in the surgical specimen although epidermoid carcinoma, grade II, had been present in the biopsy specimen. When the patient died, however, the autopsy revealed widespread metastases. The second case demonstrates the great difficulty in assessing the extent, or even the presence, of recurrent disease in the pelvis after irradiation. This patient had a total exenteration after radiation therapy for an epidermoid carcinoma grade II diagnosed from a biopsy specimen. The exenteration was performed for a suspected recurrence visualized on cystoscopy, but none was found either in the surgical specimen or at the autopsy. There was, however, an extensive irradiation reaction seen in all pelvic tissues.

On the contrary, neoplastic disease was often found to be more extensive than expected in the pathologic specimen from the definitive operation. This was particularly true in the patients not previously treated. Upward extension of the cervical cancer into the endometrium and myometrium, although not externally apparent, occurred often, as did spread to the vagina.

Cancer involved the paracervical tissues in 6 of the 18 cases in which Wertheim hysterectomy with or without node dissection was performed. The bladder was involved in two-thirds of the anterior and total exenteration cases and the rectum in approximately one-half of the total exenteration specimens. In the surgical material from the definitive operation (Table I), microscopic lymphatic invasion exclusive of lymph node involvement was present in 29 cases, and blood vessel invasion in 22 cases. Frequently both were seen in the same section. Histologic evidence of radiation effect was seen in 20 of 31 patients who had had preoperative radiation, but the changes were quite variable in location and degree.

Because clusters of cervical cancer cells so often lie within artefactual spaces, it is at times difficult to determine with certainty whether or not tumor cells lie within preexisting lymphatic and blood vascular spaces. In order to reduce this diagnostic problem to a minimum, tumor was only considered to be within lymphatics when it was seen in perineural spaces or adjacent to, or within, the walls of large arteries or veins. Obvious blood vessel invasion was seen in a few tissue sections reviewed during this study, but when only the hematoxylin and eosin stain is used it is often difficult to determine if tumor lies within a blood vessel or a tissue space. Special stains which delineate the persisting elastic tissue of blood vessels invaded by tumor are quite helpful in making this determination, but only a few such special stains were available in the material reviewed for this study.

PREOPERATIVE URINARY TRACT FINDINGS

A summary of preoperative intravenous pyelograms is shown in Table II. In this tabulation, with abnormal findings arranged according to the type of definitive surgery performed, it is not surprising that most of the abnormal intravenous pyelograms were seen in the cases in which the most extensive surgical procedures had been performed, i.e., cases of the most extensive disease. It is perhaps of more interest to note the rather high number of cases in which this index of renal function was within normal limits.

TABLE II.—ABNORMAL URINARY TRACT FINDINGS REVEALED BY INTRAVENOUS PYELOGRAPHY PRIOR TO DEFINITIVE SURGERY IN 55 CASES

	Wertheim	*Wertheim with lymphadenectomy*	*Anterior exenteration*	*Total exenteration*
Hydronephrosis, unilateral	0	1	1	2
Nonfunctioning kidney, unilateral	0	1	1	5
Hydronephrosis or nonfunctioning kidney, unilateral and diminished function, other side	0	1	0	1
Hydronephrosis, bilateral	1	0	0	5
Kidney function, poor, bilateral	0	0	0	1
Negative intravenous pyelograms	2	12	5	16

With the application of other diagnostic procedures, however, particularly cystoscopy and associated bacteriologic studies, additional evidence of upper and lower urinary tract disease was found more often. In 23 of the 55 cases, bladder edema was noted at observation cystoscopy, and in 7 others tumor involvement of the bladder mucosa was seen. A clinical diagnosis of pyelonephritis or cystitis was made in 14 cases, usually with culture of pathogenic organisms from the urine of bladder, ureter, or renal pelvis. Markedly elevated nonprotein nitrogen levels were also found in 5 cases.

In 5 patients who had subsequently undergone either anterior or total exenterations, urinary tract fistulas were present prior to these operations. Since most of these patients had had previous irradiation or surgical therapy, it is not possible to say whether the fistulas were the result of recurrent tumor, of therapy, or of a combination of the two.

AUTOPSY FINDINGS

Urinary tract. At autopsy, as in the preoperative evaluation of these 55 cases, gross and microscopic abnormalities were seen

TABLE III.—PATHOLOGIC FINDINGS IN URINARY TRACT AT AUTOPSY IN 55 CASES

Cases involved	*Wertheim 3/3**	*Wertheim with lymphadenectomy 10/15*	*Anterior exenteration 6/7*	*Total exenteration 27/30*	*Total 46/55*
Hydronephrosis	2	10	5	25	42
Pyelonephritis or other urinary tract infection	1	7	4	21	33
Ureteral obstruction	1	4	4	22	31
Urinary fistulas	1	3	2	11	17
Lower nephron nephrosis	0	0	0	7	7
No lesions in urinary tract	0	5	1	3	9

*3 of 3 cases.

more frequently in the urinary tract than in any other system (Table III). Unilateral or bilateral hydronephrosis was present in 42 cases. In most instances it was associated with compression of the ureter by tumor or by scar tissue either near the junction of ureter and bladder in the post-Wertheim cases or at the anastomotic site between ureter and colon in the exenteration cases. Pyelonephritis was often associated with the hydronephrosis, although it was also found in the absence of hydronephrosis. Vesicovaginal fistulas were seen in 3 cases after Wertheim hysterectomy with pelvic lymphadenectomy, while ureteroperineal fistulas occurred in 8 cases after total exenteration.

Lower nephron nephrosis associated with oliguria or anuria occurred in 7 exenteration cases. Its cause in the different cases is difficult to determine with certainty at this time, but in several instances marked hemorrhage and prolonged periods of shock occurred during the operation and postoperatively. Numerous blood transfusions were given in each of these cases, but in no case was the renal shutdown attributed, by clinicians handling the case, to an incompatible transfusion.

Immediate cause of death. In order to compare the immediate causes of deaths during the postoperative period with those occurring later, the 55 cases have been divided into 2 groups according to whether death occurred earlier or later than 6 months after definitive surgery. Six months was selected as the dividing line between early and late deaths because none of the patients who died within this time interval had left the hospital postoperatively. The groups have been further subdivided according to the type of operation performed and the presence or absence of residual tumor at autopsy (Table IV).

Three of the early deaths were due to pulmonary embolism, a cause of death not encountered in the late group. Acute infections, or acute exacerbations of chronic ones, were responsible for 14 of the 29 deaths in the early group and for 8 of the 26 deaths in the late group. In most of these cases peritonitis, pelvic abscess with septicemia, or pyelonephritis and pyonephrosis were the anatomic causes of death. To lesser degrees, of course, these and other types of sepsis were also seen in other cases in which they were not of sufficient magnitude to be listed as the cause of death.

Uremia was the cause of death in 3 cases in the early group. In all 3 it was secondary to anuria in the first few postoperative days. In the late group, uremia was the cause of death in 5 cases, in all of which Wertheim operations with or without node dissection were performed. Residual tumor was present in 4, with ureteral compression by tumor in 3 of them. In the fourth case there was no anatomic evidence of urinary tract obstruction, and uremia apparently resulted from functional renal inadequacy. The 1 patient who died of uremia but was free of tumor at autopsy had bilateral ureteral stenosis, presumably secondary to the operative procedure, and a pronounced upper urinary tract infection.

Extensive local and metastatic spread of cancer was considered the cause of death in 2 total exenteration cases during the first 6 months, and in 8 cases after the 6 month postoperative period had passed. Four of these late deaths were in total and 1 in an-

TABLE IV.—IMMEDIATE CAUSE OF DEATH

	Wertheim		*Wertheim and nodes*		*Anterior exenteration*		*Total exenteration*		
	Residual tumor		*Residual tumor*		*Residual tumor*		*Residual tumor*		
	Neg.	*Pos.*	*Neg.*	*Pos.*	*Neg.*	*Pos.*	*Neg.*	*Pos.*	*Total*
	29 PATIENTS SURVIVING LESS THAN 6 MONTHS								
Peritonitis and other infection	0	0	1	1	1	0	6	5	14
Uremia	1	0	0	0	0	0	1	1	3
Spread of tumor	0	0	0	0	0	0	0	2	2
Hemorrhage	0	0	0	0	2	0	1	0	3
Pulmonary embolism	0	0	2	0	1	0	0	0	3
Miscellaneous	0	0	0	0	0	0	4	0	4
Total	1	0	3	1	4	0	12	8	29
	26 PATIENTS SURVIVING MORE THAN 6 MONTHS								
Peritonitis and other infection	0	0	0	1	1	1	0	5	8
Uremia	0	1	1	3	0	0	0	0	5
Spread of tumor	0	1	0	2	0	1	0	4	8
Hemorrhage	0	0	0	1	0	0	0	1	2
Miscellaneous	0	0	2	1	0	0	0	0	3
Total	0	2	3	8	1	2	0	10	26
Grand totals	1	2	6	9	5	2	12	18	55

terior exenteration cases, and 3 occurred in the Wertheim groups.

Massive hemorrhage was the cause of death in 5 cases. One patient died of uncontrollable hemorrhage 1 month after a total exenteration when a pelvic abscess eroded the right common iliac artery. No residual tumor was found at autopsy. Two other patients in the early group also died of hemorrhage but in both the bleeding was from the upper gastrointestinal tract and was not associated with either the tumor or the operative site. Profuse hemorrhage from a previously quiescent gastric ulcer 8 days after an anterior exenteration was responsible for 1 death. Massive hemorrhage from esophageal varices 3½ months after an anterior exenteration caused the second death. In this patient viral hepatitis had developed fairly early in her postoperative course with the subsequent formation of esophageal varices. Her poor condition necessitated prolonged intubation with a Levin tube, a therapeutic measure which may have been partially responsible for the bleeding which later occurred from an area of ulceration in the lower esophagus. No residual tumor was found in either of these 2 patients.

Massive hemorrhage also accounted for 2 deaths in the late group, and in both cases it resulted from ulceration and perforation of the bowel by recurrent tumor. In 1 case, 3 years after Wertheim hysterectomy with lymph node dissection, the sigmoid colon was involved. In the second case, 20 months after a total exenteration, tumor was found to have extended from the presacral tissue to an adherent loop of small bowel.

Residual tumor. No residual cancer was found at autopsy in 24 cases. Tumor was found in 31 cases. It was limited to the pelvis in 3, present both in the pelvis and in distant parts of the body in 19, and metastatic to distant sites only, without any pelvic recurrence, in 9 cases. The relationship between the distribution of residual tumor and the type of definitive surgical therapy is shown in Table V.

It is interesting to note that there were 2 patients treated by Wertheim hysterectomy and node dissection in whom a second primary cancer developed (3.6 per cent of 55 cases of cervical cancer). In neither case was residual epidermoid carcinoma of the cervix found, but in both there was widespread metastatic adenocarcinoma, one orig-

TABLE V.—DISTRIBUTION OF RESIDUAL TUMOR AT AUTOPSY IN 55 CASES

	Wertheim hysterectomy	*Wertheim hysterectomy with pelvic lymphadenectomy*	*Anterior exenteration*	*Total exenteration*	*Total cases*
Total No. without residual tumor	1	6*	5	12	24
Total No. with residual tumor	2	9	2	18	31
Pelvic and distant metastases	2	4	0	13	19
Distant metastases only	0	3	2	4	9
Limited to pelvis	0	2	0	1	3

*Two patients with epidermoid carcinoma of the cervix had no residual epidermoid carcinoma at autopsy, but died with widespread metastases from adenocarcinoma of stomach and lung, respectively.

inating in the stomach and one in the lung.

The location of residual tumor found outside of the pelvis at autopsy is tabulated in Table VI according to the type of definitive surgical procedure employed. The paraaortic lymph nodes were more often involved than any other lymph node group or any one organ. Lymph nodes in other extrapelvic sites were involved in a total of 17 cases, with the nodes in the pulmonary hilar areas containing tumor in 10 cases. Pulmonary involvement was found in 14 cases and hepatic involvement in 12. The relatively frequent involvement of the large intestine (10 cases) and the small intestine (9 cases) is probably explained in part by the difficulty of determining from the autopsy protocol whether there were true metastases or direct extension from residual pelvic tumor. The latter would have been particularly liable to occur in postexenteration cases in which loops of bowel are often bound by adhesions to the pelvic wall or presacral area. Similarly, the peritoneal involvement tabulated for some cases may in fact have been the result of direct extension of tumor from involved lymph nodes or previously established foci of tumor rather than true metastatic disease.

The presence of metastatic cancer in the spleen in almost 10 per cent of the cases is of interest in view of the general impression that splenic cancerous metastases are rare and also when compared with autopsy studies reported by Henriksen (4) and by Holzaepfel and Ezell. The former reports an incidence of splenic involvement in 1.6 per cent of 154 nontreated cases, and no instances of splenic involvement in 202 cases of cervical cancer treated by irradiation. The latter authors report metastases in the spleen in 7.0 per cent of 43 nontreated cases and 1.5 per cent of 64 cases of cervical cancer treated by irradiation.

Therapy, lymph nodes, and residual tumor. The relationship between the type of operation employed, the presence of positive lymph nodes in the surgical specimen, and the presence of extrapelvic metastases at autopsy is seen in Table VII. Of the 3 cases in which the Wertheim operation without node dissection was done, 2 had distant metastases.

Eight of the 15 patients treated with a Wertheim hysterectomy and lymph node dissection had positive nodes in the surgical specimen and 5 of them had distant metastases. Seven patients had negative nodes at operation and only 2 had distant metastases.

In the anterior exenteration group, 2 of 3 patients with positive nodes in the surgical specimen had distant metastases at autopsy. None of the 4 cases with negative nodes had residual tumor at autopsy.

In the total exenteration group there appears to be a generally similar, but less clear cut, relationship between positive nodes at operation and metastatic tumor at autopsy. Eleven received no preoperative irradiation. Five of them had positive lymph nodes, and 3 of these had distant metastases. Six had negative nodes, and only 2 of them had distant metastases.

Of 19 total exenteration cases with recurrent tumor after previous irradiation positive nodes were present in 13. Nine of the latter patients had metastatic tumor in distant sites. Six of the 19 with preoperative irradiation had negative nodes, but 4 of these 6 had residual disease at autopsy.

TABLE VI.—DISTRIBUTION BY ORGANS OF DISTANT METASTASES IN 28 CASES AT AUTOPSY

	Wertheim operation 2/3	*Wertheim operation with pelvic lymphadenectomy 7/15*	*Anterior exenteration 2/7*	*Total exenteration 17/30*	*Total 28/55*
Para-aortic nodes	1	2	1	11	15
Other distant lymph nodes	1	6	1	9	17
Lung	1	4	0	9	14
Liver	1	3	1	7	12
Large intestine	1	0	1	8	10
Small intestine	1	0	0	8	9
Peritoneum	2	1	0	5	8
Bone	0	2	0	5	7*
Spleen	0	2	0	3	5
Pancreas	1	1	0	3	5
Skin	0	0	0	3	3
Other sites	0	6	1	10	17

*One or more vertebrae were involved in each case.

The relationship between the type of operation performed, lymph node involvement in the surgical specimen, the presence of residual tumor at autopsy, and the length of postoperative survival is shown in Table VIII. In the group of 29 cases in which positive lymph nodes were found in the surgical specimen, all of the patients surviving the initial 6 month postoperative period had residual tumor at autopsy. On the other hand, in the group of 26 patients with negative nodes at operation 6 were found to have no residual tumor at autopsy from 6 months to 5 plus years after operation.

Residual tumor was found in all patients in the total exenteration and in 1 of the anterior exenteration groups who survived 6 months or more. No residual tumor was found in 12 of the 20 total exenteration patients who died in less than 6 months. The absence of tumor in these 12 cases probably reflects the fact that surgery which is extensive enough to remove all pelvic cancer in some cases is too much for the patient to tolerate.

TABLE VII.—RELATIONSHIP BETWEEN TYPE OF THERAPY, LYMPH NODE INVOLVEMENT AND DISTANT METASTASES

Operation	*No. of cases*	*Distant metastasis*	*No metastasis*
Wertheim without nodes	3	2	1
Wertheim and nodes	15		
Positive nodes	8	5	3**
Negative nodes	7	2	5
Anterior exenteration	7		
Positive nodes	3	2	1
Negative nodes	4	0	4
Total exenteration	30		
Positive nodes	18	12	6
Negative nodes	12	5	7*

*1 case local recurrence.
**2 cases local recurrence.

DISCUSSION

Before any conclusions are drawn from this material it should again be noted that these data are not representative of the end results of radical surgery for cancer of the female pelvis. Brunschwig and Daniel (2) report 15 per cent 5 year survivals in 111 patients with advanced cervical cancer treated by total pelvic exenteration and recent reports by Parsons and associates (10, 11) show similar results. In less advanced stages of cervical cancer the results of Meigs and others are even more favorable and are comparable with results achieved by irradiation therapy.

Not only is the present series limited to patients dying of cancer or complications resulting from its therapy, but also to those who died in hospitals. This is the group in which the complications of the disease or its treatment were so severe as to impel the patient to return to the hospital. In addition, this series includes some patients in whom both irradiation and surgical therapy failed to control the disease in its earlier stages. Thus, from all aspects, this probably constitutes the treated group with the worst possible outcome.

Collecting the information obtained by autopsy study of these cases is essential, however, if we are to understand how surgery, with or without previous irradiation therapy, alters the course of cancer arising in the uterine cervix. It is to be hoped that,

as more clinical material is accumulated in centers throughout the country, future reports of surgically treated cases will include more details from the pathologic study of both the surgical and autopsy material.

Comparison of the autopsy findings in this series with those reported to date of both untreated cervical cancer and cervical cancer treated by irradiation reveals that whether treated or untreated the major complications and the majority of deaths in cases of cervical cancer are due to urinary tract disease. It seems important, however, in attempting to determine the value of radical surgical therapy to consider the urinary tract complications in 2 categories: those secondary to recurrent cancer and those secondary to therapy itself.

When postoperative urinary tract disease is secondary to the involvement of ureters or kidneys by recurrent tumor, obviously very little reduction in morbidity or mortality can be expected with modification of surgical procedures. On the contrary, it has been amply demonstrated in recent years that in the absence of recurrent tumor the incidence of urinary tract disease after extirpation of the bladder can be markedly reduced by separating the urinary and fecal streams. Use of the ileal bladder proposed by Bricker, or the isolated sigmoid loop suggested by Parsons, when coupled with improved techniques of ureteral transplantation has resulted in a marked reduction in both immediate and late postoperative urinary tract complications. Thus, the figures given here for postoperative urinary tract complications, occurring as they did in cases in which there was a common outlet for urine and feces, may soon prove to have only historical significance.

With regard to the routes of spread taken by cervical cancer, the data from this study lead to the same conclusion reached by Henriksen (5) previously, namely, that in addition to lymphatic spread the "probability of vascular transport must be considered not only for the bizarre sites, but also for the more common deposits." From this study and others recently completed, it seems likely that blood vessel invasion at the primary site is the most common portal through which cervical cancer enters the blood stream, although, as Javert points out, there are alternate routes which may be taken.

The presence at autopsy of residual tumor in the pelvis or at distant sites in patients who survived more than 6 months after Wertheim hysterectomy with or without lymphadenectomy indicates that in those particular cases tumor was probably more extensive than could be adequately treated by the Wertheim procedure. In at least 3 of the 18 patients so treated this fact was recognized at the time of operation, according to the operative notes. In one case there was an apparently solitary mass of tumor in the omentum, which was also removed, and in another case tumor was recognized in a frozen section made from a para-aortic lymph node. In the third case tumor was left along the course of the major iliac vessels. In all of these cases it was elected to carry out the Wertheim procedure as a palliative measure. Similarly, in several cases, pelvic exenteration was performed as a palliative procedure with the knowledge that tumor was left behind.

The data from the present study reemphasize the point made by various authors that the presence of tumor in the regional pelvic lymph nodes is the pathologic finding with the most significance in the prognosis of the patient undergoing a Wertheim hysterectomy with pelvic lymphadenectomy or an anterior or total exenteration for cancer of the cervix.

Of 29 patients with positive nodes in the surgical specimen, in 21 residual tumor was present at autopsy. On the contrary, only 10 of 26 patients with negative nodes had residual tumor at autopsy, and 16 did not. However, as noted in a recent study of surgically treated cancers by Parsons, Cesare, and Friedell, the involvement of lymph nodes does not appear to be an essential intermediate stage in the dissemination of the tumor. Rather, the lymph

TABLE VIII.—POSTOPERATIVE SURVIVAL CORRELATED WITH TYPE OF DEFINITIVE OPERATION PERFORMED, LYMPH NODE INVOLVEMENT, AND RESIDUAL TUMOR AT AUTOPSY

	Wertheim hysterectomy without node dissection		*Wertheim hysterectomy with node dissection*		*Anterior exenteration*		*Total exenteration*		*Total*	
	—*Residual tumor*—		—*Residual tumor*—		—*Residual tumor*—		—*Residual tumor*—		—*Residual tumor*—	
Survival	*Neg.*	*Pos.*	*Neg.*	*Pos.*	*Neg.*	*Pos.*	*Neg.*	*Pos.*	*Neg.*	*Pos.*
	26 CASES WITH NEGATIVE NODES AT OPERATION									
Hospital death	1	0	1	1	2	0	6	2	10	3
6 mos.–1 yr.	0	0	0	1	1	0	0	2	1	3
1–2 yrs.	0	2	0	0	0	0	0	1	0	3
2–5 yrs.	0	0	3	0	1	0	0	1	4	1
5 yrs.+	0	0	1	0	0	0	0	0	1	0
Total	1	2	5	2	4	0	6	6	16	10
	29 CASES WITH POSITIVE NODES AT OPERATION									
Hospital death	0	0	1	1	1	1	6	6	8	8
6 mos.–1 yr.	0	0	0	2	0	0	0	4	0	6
1–2 yrs.	0	0	0	2	0	1	0	1	0	4
2–5 yrs.	0	0	0	1	0	0	0	1	0	2
5 yrs.+	0	0	0	1	0	0	0	0	0	1
Total	0	0	1	7	1	2	6	12	8	21
Group total	1	2	6	9	5	2	12	18	24	31

node involvement is interpreted as an indication that the tumor has reached the particular stage in its biologic development at which time it has begun to spread beyond its primary site via one or more alternate routes. The fact that a 5 year cure rate of 50 per cent was found in 6 stage I cases with positive nodes may be explained by postulating that spread via lymphatics to regional nodes was the first and only route followed in these cases. Brunschwig and Daniel report a 5 year cure rate of 61 per cent in 18 stage I cases with positive nodes.

As the volume of tumor at the primary site, and therefore the clinical stage, increased in the series reported by Parsons and associates (10) other routes of dissemination were also apparently followed. Thus, in stage II, the 5 year cure rate was only 12.5 per cent (1 of 8 cases) when positive nodes were found at operation, and, in stages III and IV, there were no 5 year survivals in the positive node group.

SUMMARY

The significant autopsy findings have been reported in 55 patients with carcinoma of the cervix who were treated by Wertheim hysterectomy in 3 cases, Wertheim hysterectomy plus pelvic lymphadenectomy in 15 cases, anterior pelvic exenteration in 7 cases, and total pelvic exenteration in 30 cases. The preoperative clinical assessment of the extent of disease was made more difficult in some cases by the reaction to previous irradiation therapy, but, even without this factor, pathologic study of the surgical specimen showed that such assessment was frequently inaccurate. Lymphatic invasion at the primary tumor site was noted in slightly more than half of the cases, and blood vessel invasion in slightly less than half. The presence of positive lymph nodes in the surgical specimen was the most important prognostic feature regarding the presence of residual tumor at autopsy.

In this study, as in others previously reported, positive lymph nodes in the operative specimen appeared to indicate dissemination of tumor by other routes as well as by lymphatics to regional nodes. With an increasing volume of tumor at the primary site, positive lymph nodes were of increasing

importance in indicating the probable presence of metastatic cancer at autopsy.

Urinary tract complications, both preoperatively and postoperatively, provided the most frequent problems in the clinical management of these patients and were partially or wholly responsible for a majority of the postoperative deaths. Such complications should be much fewer in the future as surgical techniques improve, especially in anterior or total exenteration cases. Urinary tract complications due to recurrent tumor, however, will undoubtedly continue to be seen in later stages of the disease.

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HUMAN CARTILAGE GRAFTS STORED IN AIR

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HOMOGENOUS CARTILAGE was selected for investigation because of the great demand for a supporting material for the correction of contour defects. In order to examine the long-term supporting effectiveness of both viable and nonviable homogenous cartilage, storage media were selected to produce cellular death or to support viability. After these several methods of storage, transplantation into volunteers was carried out and the cartilage again examined. The general characteristics of fresh cartilage were reported in a previous article (1), as were the effects of storage in merthiolate-saline solution followed by transplantation (2), and the effects of storage in plasma followed by transplantation (3). In the present article the effects of storage of cartilage in air and of its later transplantation into volunteers are reported and the results compared with those of the previous methods.

METHODS

The methods of preparation and examination of cartilage have been previously described in detail (1). One inch segments of cartilage were placed in sterile bottles, capped, and refrigerated at 3 to 5 degrees C. After storage for varying periods of time, they were transplanted into the abdominal walls of volunteers and then removed for study.

RESULTS OF CARTILAGE STORAGE

Supravital stains. The results recorded in Figure 1 represent a total of 72 microscopic differential viability analyses of cartilage obtained from 18 cadavers, varying in age from 14 to 30 years. As noted in the graph, the average cellular viability of cartilage stored in air at 3 to 5 degrees C. was approximately 80 per cent at the end of the first month of storage, with a decline to less than 20 per cent after a lapse of 6 to 8 weeks. By the end of the third month of storage, there were no viable chondrocytes in most cases. In general, the cells which were peripherally located in the cartilaginous block tended to die much earlier than the central ones. The zones of peripheral "short-lived" cells were usually about 0.25 to 0.75 millimeter in width. In general, the normal cytoarchitecture of the tissue was preserved long after the chondrocytes became nonviable. As the stored cartilage aged and the viability decreased to from 75 to 80 per cent, there was a tendency for the viable chondrocytes to be found clumped together in relatively small areas, in groups of 15 to 30 cells, with intervening areas of nonviable cells.

Metabolic studies. One hundred and seven determinations were made on cartilage from 15 cadavers. The cartilage was stored for periods varying from 4 to 479 days. When cartilage was stored in air at 3 to 5 degrees C., the anaerobic glycolysis underwent a slow depression, so that at the end of approximately 140 days the values were depressed 47 per cent below the fresh value.

Histologic studies. Sixty-six sections taken from 10 cadavers were examined histologically for evidence of cellular degeneration. A comparison of determinations made after 1 week, 1 month, 3 months, and 4 months of storage (Table I) revealed a progressive decline in the percentage of normal cells, reaching 0 percent at the end of 4 months,

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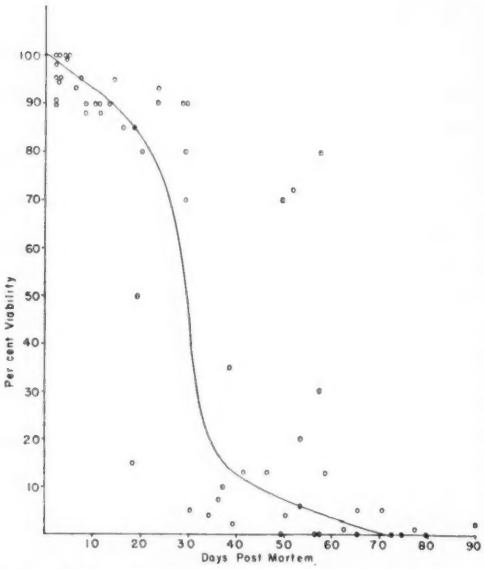

FIG. 1. Chondrocyte viability as determined by supravital staining.

with increasing cell deterioration during this period.

RESULTS OF TRANSPLANTED CARTILAGE PREVIOUSLY STORED IN AIR

Supravital stains. Cartilage blocks which had been transplanted into 10 recipients for intervals varying from 170 to 942 days manifested an average value of 55 per cent over-all viability (Table II).

Metabolic studies. Thirty-five determinations were made on air-stored cartilage which had been transplanted into 10 volunteers for 170 to 942 days. The mean anaerobic glycolysis ($Q_G^{N_2}$) was +0.043. This was 81 per cent of the normal value.

Histologic studies. Histologic examinations were made on 26 pieces of air-stored cartilage which had been transplanted into 10 volunteers for periods of 170 to 942 days. There was an average of 14 per cent normal cells, 34 per cent pyknotic, 33 per cent karyolytic, and 19 per cent "dropped-out" cells (Table II). Fibrous tissue islets, measuring central areas only, averaged 0.19 per cent of the total cross-sectional area. There was no infiltration by lymphocytes or macrophages.

Electrolyte and water exchange. Thirteen analyses each of sodium, potassium, and water content were made on air-stored cartilage which had been transplanted into 7 volunteers for 447 to 942 days (Table III). As compared with fresh cartilage, the sodium content of transplanted cartilage increased by 60 per cent, the potassium content decreased by 70 per cent, and the water content increased by 20 per cent.

TABLE I.—AVERAGE VALUES

Stored	*Per cent normal*	*Per cent pyknotic*	*Per cent karyolytic*	*Per cent "dropped-out"*
Control*	33	35	12	20
1 week	11	34	28	27
1 month	9	31	24	36
3 months	2	37	19	42
4 months	0	44	17	39

*These values represent an average of 20 specimens from fresh cadavers as reported previously (1).

DISCUSSION

Cartilage stored in air became nonviable after 3 to 4 months of storage. During this period, the $Q_G^{N_2}$ values were quite variable but represented a general downward trend. The wide range of values may reflect the inability of the acid metabolites to diffuse out of the cartilage since it was stored in a nonliquid environment. Histologic examinations revealed a progressive cellular degeneration which roughly paralleled in degree the loss of viability by supravital staining. Since the medium of storage was not liquid, there were no remarkable shifts of electrolytes and water.

Compared with cartilage stored in merthiolate and plasma, air-stored cartilage maintains its viability for the longest period of time. In addition, the electrolyte and water shifts were minimal, merely reflecting the slight (10 per cent) loss of water which occurred by evaporation during the storage period. In liquid environments of plasma or merthiolate, there was so marked an alteration of the chemical constituents of the tissue that viability could not be expected to continue. However, electrolyte exchange could

TABLE II.—TRANSPLANTED CARTILAGE (AIR-STORED)

Age in years		Days		Per cent		Per cent	Per cent	Per cent	Per cent	Total	Central
Donor	Recipient	Stored	Transplanted	viable	$Q_{O_2}^{N_2}$	normal	pyknotic	karyolytic	"dropped-out"	area*	fibrous tissue*
25	30	4	170	90	+0.019	6.5	62	24.3	8.3	47.61	0
31	47	13	198	0	+0.074	0	12.8	46.8	40.5	149.26	.463
36	50	21	261	40	—0.033	6	33	22.7	38.3	30.80	0
26	65	166	447	0	+0.033	0	0	55	45	90.20	.345
25	2½	6	734	7.5	+0.043	30.5	30.8	28.8	12.5	38.10	.060
26	22	6	740	82.5	+0.062	36	35	25	4	57.65	0
30	50	19	743	90	+0.039	25	34.5	29.5	11	94.16	.406
25	30	4	889	80	+0.048	24	36	26	14	72.90	0
25	30	4	942	70	+0.106	4	36.5	48	11.5	35.12	0
26	30	3	942	85	+0.042	10	57	25	8	51.90	0
Average values											
26	36	25	607	55	+0.043	14.2	33.8	33.1	19.3	66.77	.1274

*=cm.² Per cent total central fibrous tissue, .19.

TABLE III.—SALT AND WATER VALUES IN HUMAN COSTAL CARTILAGE

Condition of cartilage	No. of determinations	Days stored	Days transplanted	Na mEq./kgm.	K mEq./kgm.	Per cent H_2O
Fresh	64	—	—	172.46	20.3	60.8
Stored in air and transplanted	13	30	777	228.24	6.32	67.8

TABLE IV.—COMPARISON OF AVERAGES FOUND IN TRANSPLANTED CARTILAGE

Storage medium	Age in years		Days		Per cent viable supravital stain	$Q_{O_2}^{N_2}$	Per cent normal and pyknotic	Per cent central fibrous tissue
	Donor	Recipient	Stored	Transplanted				
Merthiolate	20	29	19	531	0.0	+0.069	8.8	0.76
Plasma	29	29	19	549	32.8	+0.070	32	0.50
Air	26	36	25*	607	55	+0.043	48	0.10

*This figure is high because of 1 case (166 days), without which it would be 9 days.

have taken place between the intracellular and extracellular compartments of air-stored cartilage and not have been reflected in these studies.

Supravital staining indicated that more than half of the cells of the transplanted cartilage were viable after long periods in the human host. The anaerobic glycolysis values were also high, averaging 80 per cent of the value for fresh cartilage. Histologic studies revealed about half the cells to be in the normal and pyknotic groups and the central fibrous tissue to be 0.19 per cent of the total cross-sectional area. Since fresh cartilage exhibited 0.093 per cent "fibrous tissue" areas (1), the final adjusted value for percentage of fibrous tissue invasion of total cross-sectional area would be approximately 0.1 per cent.

Despite the diversity of electrolyte shifts exhibited by cartilage stored in merthiolate, plasma, and in air, the electrolyte patterns after transplantation were remarkably similar. The low potassium contents probably indicate that the surviving chondrocytes may have been damaged to the extent that there was considerable potassium loss. Since all of these groups of transplanted cartilage exhibited varying degrees of viability and fibrous tissue invasion, the similar electrolyte patterns probably reflect the effect of the *p*H of the host upon the chondroitin sulfate-protein complexes. This theory is supported by the observation that most of the electrolyte shifts observed in these studies are presumed due to variation in the amount of bound electrolyte (2). In addition, the quantity or quality of the cation binding proteins in these three groups of cartilage studied is quite similar despite the marked differences in the three storage media.

In comparison with transplanted cartilage stored in merthiolate or plasma (Table

IV), it is evident that transplanted cartilage stored in air has the greatest viability, the most normal histologic appearance, and the least invasion by the host as seen by the minimal central fibrous tissue invasion and the nearly normal metabolic findings. It appears that the loss of viability of transplanted stored-in-air cartilage is little affected by the period of transplantation.

Although the amount of central fibrous tissue invasion was not great in any of the varieties studied, the differences were rather marked. In addition, the rate of invasion would be expected to accelerate with time, greatly increasing the differences.

CONCLUSIONS

Human cartilage stored under sterile conditions in air at 3 to 5 degrees C. appeared to maintain its viability longer than cartilage stored in merthiolate-saline solution or plasma.

After long periods of transplantation in the abdominal walls of human hosts, cartilage previously stored in air had more viable cells and a more normal histologic picture than cartilage stored in merthiolate or plasma. In addition, the host invasion of this cartilage was least of all three storage methods by both direct measurement and respiratory studies.

From this pilot study two conclusions are drawn: (1) cartilage stored in air is attended by the longest viability of all methods compared; (2) viable homogenous cartilage is less invaded by the host than nonviable homogenous cartilage and is, therefore, the more suited for surgical use.

SUMMARY

Homogenous cartilage was studied in its fresh state, after periods of storage in merthiolate, plasma, and in air, and after such storage was studied following periods of transplantation in human hosts. The examinations carried out included supravital stains, metabolic studies, histologic examinations, and electrolyte and water exchanges.

Cartilage stored in air appeared to maintain its viability for the longest period of time as compared with the other methods studied. In addition, viable cartilage maintained its viability to a considerable extent after long periods of transplantation and was associated with the least invasion by the host. From this pilot study, it appears that viable homogenous cartilage is superior to nonviable cartilage for surgical use.

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SARCOMA OF THE STOMACH

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ALTHOUGH malignant tumors of the stomach other than carcinomas comprise a relatively small percentage of the neoplasms occurring at this site, they respond to surgery and to roentgen therapy with considerably greater success than carcinomas. Because many types of gastric sarcomas remain localized for long periods of time without evidence of distant metastases, they assume a position of real surgical importance. A large, extensively spread tumor of the stomach assumed to be a hopelessly inoperable carcinoma might be a sarcoma, which, though it could not be removed, might be sensitive to irradiation. No exploratory incision for gastric neoplasm should be closed, no matter how extensive the growth, without a biopsy.

A classification of mesenchymal tumors of the stomach is given together with their differential diagnosis. An analysis of 20 consecutive patients who suffered from primary sarcoma of the stomach and were treated at The Johns Hopkins Hospital during the 10 years, 1944 through 1953, is presented.

CLASSIFICATION

Sarcomas arise from the mesenchyme as opposed to carcinomas which are epithelial tumors arising from the mesothelium. Roughly 10 per cent of all gastric tumors are of mesenchymal origin. If this group of 10 per cent is further subdivided, 60 to 70 per cent of mesenchymal tumors are benign, and 30 to 40 per cent are malignant. Therefore, about 3 to 5 per cent of all tumors arising in the stomach are malignant ones of mesenchymal origin.

Mesenchymal tumors of the stomach, both benign and malignant, are neoplasms arising from all the various components of the gastric wall, exclusive of the surface lining, i.e., from muscle, connective tissue, fat, nerve, blood vessels, and lymph vessels. On the basis of physical characteristics, treatment, and prognosis, these gastric sarcomas may be divided into two main groups, those arising from lymphoid cells and those not arising from lymphoid cells. The lymphoblastic tumors are designated in Table I under A, and the nonlymphoid tumors are designated under B through F.

LYMPHOID SARCOMA

Lymphosarcoma is the most common sarcoma of the digestive system. It comprises 60 to 70 per cent of the malignant gastric tumors of mesenchymal origin. It is radiosensitive so that, in treatment, radiation becomes an important adjunct to surgery.

Gross appearance. Lymphosarcoma tends to infiltrate diffusely throughout the submucous and muscular coats. The gastric wall becomes irregularly thickened and loses much of its pliability and functional capacity. In extreme cases, the condition of the stomach may resemble that of linitis plastica. Though lymphosarcoma may produce gastrointestinal disturbances by extrinsic pressure from enlarged retroperitoneal and mesenteric lymph nodes, it frequently produces intrinsic deformity either as a polypoid growth projecting into the lumen or, more often, as an intramural lesion that infiltrates the wall. It often appears as a large flat mass with extensive but shallow ulceration centrally.

Microscopic appearance. Lymphosarcoma can be roughly divided into: (1) large round cell sarcoma, or reticulum cell sarcoma, and (2) small round cell sarcoma, or lymphocytic sarcoma. The lymphocytic sarcomas (small cell sarcomas, malignant lymphocytomas of Madding and Walters) and reticulum cell sarcomas (large cell lymphosar-

TABLE I.—CLASSIFICATION OF MESENCHYMAL TUMORS OF THE STOMACH

Histogenesis	*Benign*	*Malignant*
A. Lymphogenous	Benign lymphoma	Lymphoblastoma (lymphosarcoma)
B. Myogenous	Leiomyoma	Leiomyosarcoma
C. Fibroblastic	Fibroma	Fibrosarcoma Myxosarcoma
D. Lipoblastic	Lipoma	Liposarcoma
E. Endothelial	Hemangioma Lymphangioma Benign hemangio-endothelioma	Malignant angioendothelioma Hemangiosarcoma
F. Neurogenous	Neurofibroma Neurilemmoma	Neurofibrosarcoma Malignant neurilemmoma

Modified after France and Brines.

comas, retothelial sarcomas) have until recently been considered slightly different varieties of lymphosarcoma. Although closely related, their origin, cell structure, and clinical behavior warrant differentiation. Lymphocytic sarcomas are composed of and appear to develop from cells resembling mature lymphocytes. In contrast, reticulum cell sarcomas arise from reticulum cells which are macrophages capable of ameboid behavior and, even in the early mesenchyme, are readily distinguishable from cells of the lymphocytic series. Individual cells vary from twice to three times the size of those of the lymphocytic type. Nuclei contain prominent nucleoli and are pale, pleomorphic, and vesicular. The cytoplasm is relatively abundant and eosinophilic. Reticular cells are scattered through a loose matrix marked by a thin reticular stroma. The reticulum is an important diagnostic criterion. To bring this out, specific stains are required. The small round cell lymphosarcoma seems to be the most radiosensitive, although tumors of the large round cell reticulum variety are known to respond to irradiation.

NONLYMPHOID SARCOMA

The great bulk of this group is made up of leiomyosarcoma and, to a lesser extent, fibrosarcoma, which will be discussed as prototypes. The remainder of the nonlymphoid group, liposarcoma, neurofibrosarcoma (also referred to as neurogenic sarcoma and neurosarcoma), hemangiosarcoma, and malignant neurilemmoma are very rare. The nonlymphoid group forms from 30 to 40 per cent of the malignant mesenchymal tumors. Because of their slow growth and late metastases, surgical prognosis is quite good. They are resistant to radiation therapy.

These tumors are originally intramural and may remain so, but more often project into the gastric interior or grow outward to form pedunculated exogastric lesions. They frequently attain a large size and are solid but may contain areas of cystic degeneration. Pressure necrosis or frank ulceration of the overlying mucosa may occur with resulting severe hemorrhage. The exogastric tumors, especially, may be massive in size. They chiefly involve the lesser curvature, usually the pyloric antrum, and rarely the pylorus and cardia. Generally, the greater portion of the stomach remains uninvolved.

Leiomyosarcoma. It is frequently difficult to distinguish between benign and malignant myomatous tumors of the stomach, either clinically or pathologically. A leiomyosarcoma may develop in a pre-existing leiomyoma. Morphologically, the tumors vary from cellular myoma to spindle cell sarcoma.

Leiomyosarcoma is a neoplasm consisting of immature smooth muscle cells of varying degrees of differentiation grouped into interlacing bundles and bands separated by a fibrous stroma, the amount of which depends on the compactness of the tumor structure. The finding of mitotic figures establishes the malignant nature of the lesion. Leiomyosarcomas vary in structure from extremely cellular myomas of questionable malignancy to the anaplastic undifferentiated tumors of high malignancy.

Fibrosarcoma. This tumor may be considered the prototype of spindle cell sarcomas. Confusion may arise because the more anaplastic forms are hard to differentiate from the anaplastic tumors of nerve sheath and smooth muscle origin. Ordinarily, fibrosarcomas are easily identified by their elongated, fusiform cells arranged in

closely packed, interlacing bundles. Nuclei which conform to the spindle shape of the cell are usually sufficiently clear-cut to differentiate this tumor from leiomyosarcoma in which the usual nuclear outline is that of a cigar. In keeping with a relatively low grade of malignancy, hyperchromatism is slight and mitotic figures sparse. The stroma shows much variation, fibrous density, and may contain many thin-walled capillaries.

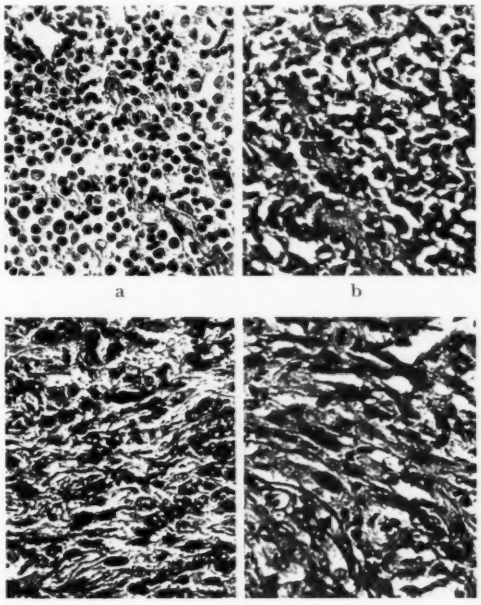

FIG. 1. a, Lymphosarcoma (small round cell type). Note the following characteristics: richly cellular, closely packed tissue resembling normal lymphoid tissue; slight pleomorphism; and infrequent mitotic figures. b, Lymphosarcoma (reticulum cell type). Note the following characteristics: larger, more regular cells with reticular fibers; pronounced pleomorphism; and frequent mitotic figures. c, Fibrosarcoma. Note the following characteristics: closely agglomerated, markedly pleomorphic cells; abundant stroma; nuclei varying greatly in size and shape; and abundant mitotic figures. d, Leiomyosarcoma. Note the following characteristics: dense masses and whorls of closely packed spindle shaped cells with scanty stroma; variation in size and shape of nuclei; frequent mitotic figures; and occasional giant cells.

ANALYSIS OF CASES

In the 10 year period from 1944 through 1953, 20 patients with primary sarcoma of the stomach were seen at The Johns Hopkins Hospital. There were 11 patients with lymphosarcomas (8 small round cell and 3 reticulum cell), 8 with leiomyosarcomas, and 1 with a neurofibrosarcoma.

The average age of these patients was 53 years, ranging from 19 to 70 years. Thirteen, or 65 per cent, were male; 14 were Caucasian, 6 were Negro.

Ten of the 20 patients complained of peptic indigestion suggestive of ulcer. The epigastric pain bore no constant relation to ingested food. Some of these patients had early disease, others advanced. Four patients complained of diffuse abdominal pain; all 4 patients had advanced disease. Three patients showed weakness or weight loss or both. Two had early disease, 1 advanced. Two patients, seen early in the disease, were asymptomatic, the diagnosis of tumor having been made by means of routine gastrointestinal x-ray examination. Only 1 patient suffered a massive hemorrhage. In this patient the tumor was found to be large but circumscribed.

The duration of symptoms ranged to 3 years. Two patients were asymptomatic, 3 patients had symptoms for less than 6 weeks, 9 patients had symptoms for a period of between 6 weeks and 6 months, 2 patients for 6 months to 1 year, and 4 patients for between 1 and 3 years.

The significant signs and symptoms consisted of: abdominal pain in 15 cases, weight loss in 12, anorexia in 10, vomiting in 8, anemia (hematocrit less than 30) in 7, melena in 5, occult blood in stools in 2, suspected mass in 4, definite mass in 3, dysphagia in 2, and hematemesis in 2.

In 18 of the 20 patients barium studies were made of the upper gastrointestinal tract. The findings were variable, but in all a mass, often stated to be intramural, was demonstrated. Some showed heaped up rugal folds, but this finding was not constant. In general, the diagnosis was "probable carcinoma" or "probable benign neoplasm." In only 1 case was sarcoma listed as the most likely diagnosis.

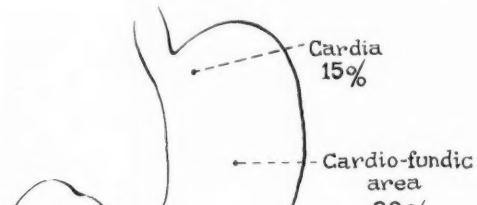

FIG. 2. Location of sarcoma.

Four patients had masses of less than 4 centimeters in diameter at the time of diagnosis. Three of these patients were free of metastases, the fourth had large periaortic nodes. All other patients had moderately large to massive neoplasms.

Three of the tumors were located predominantly in the cardia. Only 1 arose from the pyloric region. The remainder (80 per cent) were in the body of the stomach and were about equally distributed on the posterior surface, lesser curvature, and greater curvature, with only 2 on the anterior wall. Three of the leiomyosarcomas were pedunculated endogastric masses; one noted to be invading serosa. The tumors often were described as soft, but some were firm. In the cases in which lymph nodes were suspect, they were described as larger and softer than those usually found with gastric carcinoma.

TABLE II.—ANALYSIS OF 5 YEAR SURVIVORS

		5 year survivors	
	No. of patients	*No.*	*Per cent*
No treatment	1	1	100
X-ray only	2	1	50
Surgery only	12	6	50
X-ray and surgery	3	1	33
Resection			
None	3	2	67
Partial gastrectomy	11	7	64
Total gastrectomy	4	0	0

TABLE III.—CORRELATION OF 5 YEAR SURVIVORS WITH CELL TYPE

		5 year survivors	
	No. of patients	*No.*	*Per cent*
Cell type			
Lymphosarcoma	9	4	44
Leiomyosarcoma	8	5	68
Neurofibrosarcoma	1	0	0
Metastases			
No metastases	9	6	67
Local metastases	7	2	29
Distant metastases	2	1	50

Two cases were diagnosed preoperatively, one from previous surgery elsewhere and the other from x-ray characteristics. Eight cases were diagnosed at the time of exploration, 5 from a frozen section study, 2 from gross characteristics alone, and 1 on the basis of gross characteristics in spite of an incorrect diagnosis of carcinoma on frozen section. Another lesion was suspected of being sarcoma but was treated as carcinoma on the basis of that diagnosis by frozen section.

Ten patients had no demonstrable metastases. Seven had local extension either to nodes or contiguous organs. Three had distant metastases. (Leiomyosarcoma is known to metastasize by other than lymphatic channels.) As far as could be determined, 7 of our 8 patients with leiomyosarcoma were free of metastases at the time of operation, and the remaining patient had extensive distant metastases.

All patients underwent surgery: total gastrectomy in 4 cases, subtotal gastrectomy in 8, wedge resection of the stomach in 3, sleeve resection of the stomach in 1, and biopsy only in 4. One patient died 9 days postoperatively from complications of total gastrectomy—an operative mortality of 5 per cent.

Eighteen patients are included in a 5 year follow-up study, as shown on Table II. Of the 2 patients excluded from follow-up study, 1 died of heart disease 4 years postoperatively. There was no evidence of recurrent sarcoma, but autopsy was not performed. The remaining patient is completely lost to follow-up. Nine patients were alive without evidence of recurrence 5 or more years postoperatively, a 5 year survival figure of 50 per cent.

In Table III is presented a correlation of survival with cell type, metastases, and forms of treatment. Patients with a leiomyo-

sarcoma had a somewhat better survival rate than those with a lymphosarcoma. Distant metastases in instances of lymphosarcoma did not preclude 5 year survival and apparent cure. The results of total gastrectomy were disappointing within this series.

DISCUSSION AND CONCLUSIONS

The early diagnosis of sarcoma of the stomach and its differential diagnosis from carcinoma of the stomach are not easy. Sarcoma appears most frequently in patients who are 45 to 55 years old, about 10 years younger than those in whom carcinoma develops. In general, sarcoma becomes more extensive within the stomach before anemia, weight loss, and other systemic signs of malignancy become apparent. Some sarcomas attain a very large size and may be present as an exogastric tumor easily palpable through the abdominal wall.

Sarcoma may be associated with any of the roentgenographic manifestations characteristic of carcinoma of the stomach. Certain roentgenographic signs may be suggestive of sarcoma, but carcinoma may mimic any type of defect occurring in sarcoma. In this series, roentgenographic examination was diagnostic in only 1 of 18 studies. Others report a similar experience.

While carcinoma commonly occurs at the two orifices of the stomach and may lead to early signs of obstruction, sarcoma is more apt to be in the body of the stomach (80 per cent in our series). Sarcoma may be pedunculated on a narrow base, may be diffusely intramural, or multinodular. Generally, it is of a softer consistency than carcinoma. Rugae are frequently hypertrophied and stiff, as opposed to effacement of rugae seen in carcinoma. Lymph nodes with sarcoma are generally more prominent, larger, and softer than with carcinoma. A large node believed to be cancerous will more often be reported on frozen section as inflammatory in cases of sarcoma.

It is frequently stated that hematemesis is common with sarcoma. This has not been true in this series. Diagnostic consideration has been given to the young age of patients with leiomyosarcoma, but this was not substantiated here.

FIG. 3. Leiomyosarcoma. With this massive tumor, no metastases could be found at the time of operation. The patient died without evidence of recurrence 3½ years after total gastrectomy.

Fibrosarcoma is generally reported to occur with about the same frequency as leiomyosarcoma, representing 10 to 15 per cent of all gastric sarcomas. In the 10 year period covered by this report, no case of fibrosarcoma was encountered. Jordan and associates reported 21 cases of sarcoma including 6 leiomyosarcomas and only 1 fibrosarcoma. Shannon and associates, reporting a 15 year experience with cancer of the stomach, found 3 cases of leiomyosarcoma and none of fibrosarcoma.

Pathologic examination by frozen section was made in 8 cases, 2 of which were incorrectly interpreted as carcinoma. In an additional case, the single operative death, a lymphosarcoma was suspected at the first operation and a biopsy only was performed in the hope that the tumor would prove to be radiosensitive. The permanent section of this biopsy was reported as carcinoma, and total gastrectomy was then elected. The entire specimen of the stomach later revealed lymphosarcoma. It is known that some sarcomas vary greatly in microscopic characteristics from section to section. Therefore, although biopsy should be performed routinely, it should be borne in mind that a

single section biopsy is not always reliable. In a gastric neoplasm suspected of being sarcomatous, specimens for biopsy should be taken from more than one site.

That sarcomas may be slowly growing tumors is borne out by our experience with a patient who had an untreated lymphosarcoma and who remained asymptomatic for 6 years.

Treatment. Once the diagnosis is established, treatment is dictated by the cell type and extension of disease. A lymphoid sarcoma should be excised surgically. Inasmuch as it is primarily an intramural growth, it should be given a wide margin of resection. Thorbjarnarson and associates found tumor at the margin of resection in 70 per cent of cases of lymphosarcoma thought to have been completely removed. If the tumor is beyond the bounds of curative resection, x-ray therapy alone can be curative. We have had 1 such case. With this fact in mind as well as the tendency of the growth to metastasize locally, the recommendation for following most resections for lymphosarcoma with x-ray is made.

The nonlymphoid sarcomas are resistant to the effects of irradiation, and surgical excision is the only hope for cure. Both of our patients with leiomyosarcoma, presenting as a large polyp on a narrow base, were treated with wide wedge resection and are apparently cured. Subtotal or total gastrectomy was the procedure of choice in other cases. Our single experience with x-ray therapy in the nonlymphoid group was unsatisfactory, as would be expected.

Of the 4 patients subjected to total gastrectomy, one represents an operative death —death from multiple complications occurring 8 days after operation. The second who had a neurofibrosarcoma died 9 months after operation. Abdominal masses developed several months before death and the patient always presented a severe feeding problem. No autopsy was performed. The third patient died 2½ years after operation with recurrent sarcoma proved at the second operation. The fourth died 3½ years postoperatively. Although no autopsy was performed, the cause of death was almost surely a severe recurring anemia, thought to be secondary to the total gastrectomy.

The prognosis for sarcoma of the stomach has long been known to be better than that for carcinoma of the stomach. Recent reports have proved it to be considerably better than had been found in the past. In a collective series of 474 cases of lymphosarcoma of the stomach, including 34 of his own, Snoddy noted that 50 patients had survived more than 5 years, a 10.5 percentage for 5 year survival. From a valid reappraisal of the same cases, Jordan and associates concluded that 5 year survival for lymphosarcoma was at least 27 per cent, and for leiomyosarcoma, 37 per cent. Marshall and Meissner reported 5 year survival figures of 44 per cent (including cases of Hodgkin's disease). Shannon, with 9 cases of sarcoma, reported a 5 years survival rate of 56 per cent. Of the 21 patients treated more than 5 years previous to his report, Thorbjarnarson found that 9, or 43 per cent were alive after 5 years. Our own findings of 50 per cent 5 year survival correspond.

SUMMARY

An analysis is presented of 20 consecutive patients who suffered from primary sarcoma of the stomach and were treated at The Johns Hopkins Hospital during the 10 year period from 1944 through 1953.

A classification of mesenchymal tumors of the stomach is given together with a discussion of their differential diagnosis, treatment, and prognosis.

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GENERALIZED SHWARTZMAN-LIKE REACTION FOLLOWING SERRATIA MARCESCENS SEPTICEMIA IN A FATAL BURN

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IN THIS ARTICLE ARE DESCRIBED the clinical course, pathologic findings, and immunologic responses of a severely burned patient in whom there developed a blood stream invasion by Serratia marcescens, a chromogenic bacillus more commonly encountered as a pyrogen in intravenous solutions than as a pathogen. The strong probability is indicated that an ensuing endotoxemia, in the patient due to this organism, resulted in a generalized Shwartzman reaction[1] sensitization. This reaction, evidenced by the histologic appearance at postmortem examination of the kidneys of the patient, has been described previously in lower animals. To our knowledge this is the first report of such generalized tissue reactivity in man involving Serratia marcescens.

Chromobacteria are ubiquitous, saprophytic organisms that propagate in water, soil, and milk but are rarely involved in infectious processes in humans. The prototype of this group of bacteria is Serratia marcescens, toxonomically related to the coliform organisms and the producer of a red pigment called prodigiosin.

A review of the literature on the subject of Serratia reveals that Bizio as early as 1823 showed Serratia responsible for red-colored polenta (mush) of Italian peasants. Woodward and Clark in 1913 described a patient with chronic, nonfatal pulmonary disease due to Serratia marcescens. During World War II, inhalation of this chromogen by 4 technicians in a laboratory accident at Fort Detrick described by Paine resulted in an acute influenza-like episode in these individuals. Bacteremia was not demonstrated in any of the patients of the foregoing reports.

That Serratia can invade the blood stream, however, is documented by the report of Wheat, Zuckerman, and Rantz who observed the occurrence of bacteremia following urinary tract infection in 2 of 12 patients, in 1 of whom fatal endocarditis subsequently developed.

Serratia marcescens endotoxin is a powerful oncolytic agent for certain tumor tissues. Sarcoma No. 37 implants in mice are spontaneously necrotized by as little as 10 micrograms of this material. Although this same concentration of endotoxin is locally Shwartzmanogenic for rabbits, a single dose of considerably greater potency administered intravenously produces no pathologic condition at all in these animals.

In 1952, Thomas and Good (13) described a generalized Shwartzman reaction in rabbits due to 2 spaced intravenous injections of Serratia marcescens endotoxin that resulted in occlusion of the glomerular circulation of these animals by deposition of a homogenous eosinophilic material in the glomerular capillaries. More recently, Thomas, Brunson, and Smith (10) reported production of the same histologic renal lesions in rabbits with a single injection of Serratia marcescens endotoxin followed by the injection of one of the synthetic heparin-like, acidic polymers such as dextran sulfate.

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[1]The Shwartzman reaction is a phenomenon of local tissue reactivity in the skin (localized) and various organs (generalized) of animals usually to bacterial filtrates. The local reaction is elicited by a preparatory intradermal injection of active substance followed by an intravenous injection of homologous or heterologous material 24 hours later which produces a severe hemorrhagic necrosis at the site of the intradermal injection. The generalized reaction results from 2 intravenous injections of active substance which may be homologous or heterologous with the resulting organ lesions which have been described in this article.

CLINICAL SUMMARY

A 43 year old soldier was burned on 17 October 1958 in a butane gas explosion. He sustained a 90 per cent total body surface burn, 65 per cent being full-thickness skin destruction. He was admitted to the U. S. Army Hospital at Fort Polk, Louisiana, where resuscitation was instituted, a tracheotomy was accomplished, tetanus toxoid was administered, and the patient was given prophylactic penicillin and streptomycin. He was evacuated on the day of burn to the U. S. Army Surgical Research Unit, Brooke Army Medical Center, Fort Sam Houston, Texas. Initial examination revealed the patient undergoing satisfactory resuscitation and in good clinical condition for the extent of burn. Figure 1 records the variations in his vital signs, fluid balance, and laboratory determinations during his course in the hospital.

On the first postburn day, he was taken to the operating room and under general analgesia, his burns were washed with detergent solution, cleansed with saline, and gently debrided. Cultures of the burned areas taken at that time subsequently grew alpha and enterococcic streptococci as well as Serratia marcescens. During this day, the patient was well oriented and co-operated through all procedures. His lungs remained clear. Bowel sounds were not present.

On the second postburn day, the patient was noted to have subcutaneous emphysema around the neck and upper anterior portion of the chest wall which was thought to be due to the tracheotomy. Bowel sounds had returned, and oral fluid administration was started. Cultures of the burned skin surfaces were positive for Serratia marcescens and alpha hemolytic streptococci.

On the third postburn day, the lungs remained clear, and peripheral edema about the burn wounds was diminishing. The patient remained mentally clear, bowel sounds were good, and a voluntary oral intake of 2,800 cubic centimeters was accomplished. He tolerated turning on a Stryker frame well, and only a minimal amount of secretion was suctioned from the tracheotomy tube. The patient was given 10 cubic centimeters of immune globulin intravenously after dilution in 500 cubic centimeters of 5 per cent glucose in water.

On the fourth postburn day, the patient tolerated a full liquid diet. He was well oriented, lungs were clear, and the eschar was becoming desiccated. His temperature, although elevated in the early morning hours to 101 degrees F., began to drop reaching 97.5 degrees F. rectally at 10 p.m. He exhibited slight cyanosis and endotracheal oxygen was started. Serratia marcescens was cultured from the urine at this time. He was given 10 cubic centimeters of gamma globulin intravenously.

On the fifth postburn day the respiratory difficulties became more marked. There was a prolonged expiratory phase with wheezes and rales at this time. There was poor aeration in the bases. The patient was given 500 milligrams of aminophylline intravenously with slight improvement. Roentgenogram of the chest showed patchy infiltration of all lung fields. During the early morning hours the patient's temperature was approximately 99 degrees F. but subsequently fell progressively. A blood culture taken at this time grew out Serratia marcescens in each of 3 media employed. His respirations progressively deteriorated, he became cyanotic, and intermittent positive pressure breathing with 100 per cent oxygen was instituted. His blood pressure fell and levarterenol bitartrate was necessary to maintain a systolic of 80 millimeters of mercury. Cortisone in amount of 400 milligrams was administered intravenously. The demand for support by levarterenol bitartrate increased rapidly, and a concentration of 16 ampules per liter was required prior to death. His urinary output fell progressively with his temperature which was 90 degrees F. at noon. A hypothermia blanket with hot solution (108 degrees F.) running through the coils was placed on the patient, and this raised his temperature to 92 degrees F. The patient expired at 2 p.m. A blood culture was taken immediately by cardiac puncture. This culture, and one subsequently obtained at autopsy, were positive for Serratia marcescens.

Postmortem findings. With the exception of thermal injury to the skin, significant pathologic findings were limited to the genitourinary system. Each kidney had approximately the same gross and microscopic appearance. Each weighed approximately 250 grams, was pale in color, and moderately soft in consistency. Almost all the glomeruli were similar in appearance. The individual glomerulus was composed of a thin-walled endothelium-lined, capillary network that appeared moderately distended with minimal amounts of red blood cells and moderate amounts of homogenous eosinophilic material arranged in strands or fibers conforming to the general configuration of the glomerular tuft (Figs. 2, 3, and 4). The glomerular space was devoid of any proteinaceous material or red cells. Both the proximal and distal tubules of the cortex showed moderate desquamation of individual cells and pyknosis of the nuclei. The medullary portions of the kidney showed no recognizable changes except moderate amounts of blood engorging the capillary network. Occasionally, small amounts of bright eosinophilic homogenous material, much deeper in color however than that seen in the glomeruli, were seen within the collecting tubules and were interpreted as proteinaceous casts. The small arterioles within the cortex revealed only minimal sclerosis. The pelvis contained small amounts of blood in which only an occasional granulocyte was seen. No inflammatory reaction in either the cortex or medullary portions of the kidney was observed.

The homogenous eosinophilic material engorging the glomerular capillary tufts when stained with orange G was light yellowish-orange in color. When

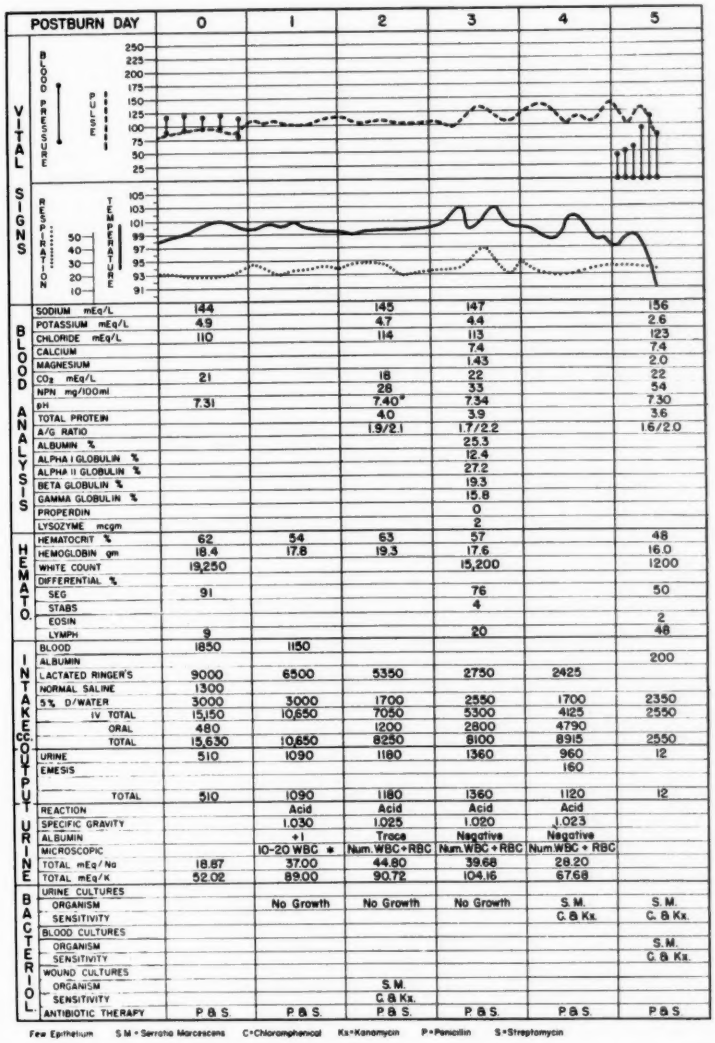
POSTBURN DAY
0
1
2
3
4
5
VITAL SIGNS
BLOOD PRESSURE
PULSE
RESPIRATION
TEMPERATURE
BLOOD ANALYSIS
SODIUM mEq/L 144 145 147 156
POTASSIUM mEq/L 4.9 4.7 4.4 2.6
CHLORIDE mEq/L 110 114 113 123
CALCIUM 7.4
MAGNESIUM 1.43 2.0
CO2 mEq/L 21 18 22 22
NPN mg/100ml 28 33 54
pH 7.31 7.40* 7.34 7.30
TOTAL PROTEIN 4.0 3.9 3.6
A/G RATIO 1.9/2.1 1.7/2.2 1.6/2.0
ALBUMIN % 25.3
ALPHA I GLOBULIN % 12.4
ALPHA II GLOBULIN % 27.2
BETA GLOBULIN % 19.3
GAMMA GLOBULIN % 15.8
PROPERDIN 0
LYSOZYME mcgm 2
HEMATO.
HEMATOCRIT % 62 54 63 57 48
HEMOGLOBIN gm 18.4 17.8 19.3 17.6 16.0
WHITE COUNT 19,250 15,200 1200
DIFFERENTIAL %
SEG 91 76 50
STABS 4
EOSIN 2
LYMPH 9 20 48
INTAKE cc.
BLOOD 1850 1150
ALBUMIN 200
LACTATED RINGER'S 9000 6500 5350 2750 2425
NORMAL SALINE 1300
5% D/WATER 3000 3000 1700 2550 1700 2350
IV TOTAL 15,150 10,650 7050 5300 4125 2550
ORAL 480 1200 2800 4790
TOTAL 15,630 10,850 8250 8100 8915 2550
OUTPUT
URINE 510 1090 1180 1360 960 12
EMESIS 160
TOTAL 510 1090 1180 1360 1120 12
URINE
REACTION Acid Acid Acid Acid
SPECIFIC GRAVITY 1.030 1.025 1.020 1.023
ALBUMIN +1 Trace Negative Negative
MICROSCOPIC 10-20 WBC * Num. WBC + RBC Num. WBC + RBC Num. WBC + RBC
TOTAL mEq/No 18.87 37.00 44.80 39.68 28.20
TOTAL mEq/K 52.02 89.00 90.72 104.16 67.68
BACTERIOL.
URINE CULTURES
ORGANISM No Growth No Growth No Growth S.M. S.M.
SENSITIVITY C. & Kx. C. & Kx.
BLOOD CULTURES
ORGANISM S.M.
SENSITIVITY C. & Kx.
WOUND CULTURES
ORGANISM S.M.
SENSITIVITY C. & Kx.
ANTIBIOTIC THERAPY P & S. P & S. P & S. P & S. P & S. P & S.
Few Epithelium S.M. = Serratia Marcescens C=Chloramphenicol Kx=Kanamycin P=Penicillin S=Streptomycin

FIG. 1. B. N., male, aged 43 years, weight 84 kilograms, total burn 89 per cent, third degree burn 65 per cent. Vital signs, laboratory data, and intake and output measurements of patient.

periodic acid Schiff's stain was used, this material appeared bright orange-green. Colloidal iron stained sections revealed the material to be deep red, almost port wine in color and black with phosphotungstic acid hematoxylin stain.

Although the homogenous eosinophilic material seen within the glomerular capillaries was not identified with certainty, chemical studies have shown that hemacetyl, 1,2 glycol free aldehyde groups are present as the reactive groups or are converted to these groups during the histochemical preparation. From the staining reaction and microscopic morphology, this material was most likely fibrin.

Focal areas of hemorrhage in the bladder mucosa diffusely infiltrated with moderate numbers of lymphocytes were seen.

Minimal bronchitis, atelectasis, and emphysema were present in the lungs. Numerous lymph nodes examined were essentially normal except for moderate reactive hyperplasia. The bone marrow revealed a

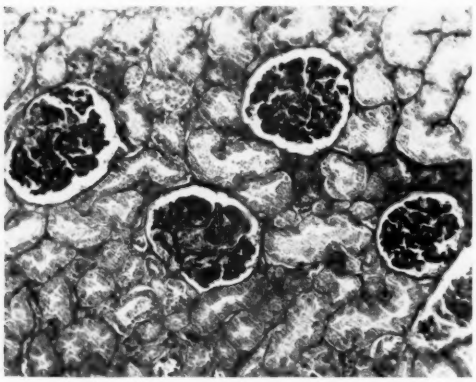

FIG. 2. Renal tissue (low power) involvement of all glomeruli with fibrin is shown (phosphotungstic acid-hematoxylin stain).

normal ratio of myeloid to erythoid elements. Arterioles of other organs studied by multiple section revealed only minimal to moderate atherosclerotic changes.

BACTERIOLOGIC AND IMMUNOLOGIC STUDIES

Examination in the bacteriologic laboratory revealed that the organisms recovered from the blood stream, from the urine, and the skin surface were similar biotypes; all were small, motile, aerobic, gram-negative, nonsporulating, anaerogenic rods that produced characteristic red colonies at room temperature. This bacillus grown in broth was insensitive to high concentrations (greater than 25 micrograms) of chloramphenicol, novobiocin, oxytetracycline, polymyxin B, penicillin, streptomycin, and erythromycin. It was, however, sensitive to 6.2 micrograms per milliliter of kanamycin.

TABLE I.—EFFECT OF TWO SPACED INTRAVENOUS INJECTIONS OF SERRATIA ENDOTOXIN AND SUCCESSIVE INJECTIONS OF ENDOTOXIN AND DEXTRAN ON RABBITS

Endotoxin	*P.S. polymer*	*No. of rabbits*	*No. dead*	*Kidney lesions*
1. Single I.V. injection of S.M. endotoxin (100 mcgm.)	—	1	0	0
2. Two spaced (8 hrs.) I.V. injections S. M. endotoxin (100 mcgm.)	—	2	2	2
3. —	Dextran (10 mgm.)	1	0	0
4. I.V. injection S.M. endotoxin	Dextran* (10 mgm.)	2	1	1

*Given 30 minutes after endotoxin injection.

Serum from the patient taken on the day of death was titered against a somatic antigen prepared by treating the patient's organisms with heat and absolute alcohol. This serum possessed a bacterial agglutinin titer of 1:16 for this antigen. Sheep red blood cells sensitized with Serratia polysaccharide that was eluted by sodium hydroxide and heat from the same organism provided a hemagglutination titer of 1:32. Sera from several laboratory workers, including one of us (C.D.G.), who have frequently worked in the laboratory with Serratia bacteria were run concomitantly for bacterial agglutinins and hemagglutinins, and no demonstrable titer was present with either antigen in these individuals.

Serratia endotoxin was prepared by treating the patient's organisms with trichloracetic acid followed by ethanol precipitation and dialysis. This substance, 100 micrograms per 0.1 milliliter, injected into rabbits proved Shwartzmanogenic for these animals. Because endotoxin of gram-negative bacteria is considered to be a part of the somatic or Boivin antigen it was of interest to determine if antibody to this fraction present in the patient's serum (1:16) would abort the Shwartzman reaction when a serum mixed with endotoxin was used for this testing. Decimal dilutions of endotoxin and undiluted patient serum still produced a typical local reaction.

The injection of the endotoxin into the surgically isolated renal circulation of the rabbit followed in 18 hours by an intravenous evoking dose of endotoxin produced death in the animal that showed at postmortem examination the homogenous eosinophilic depositions in the kidney that were identical with the stained material described by Thomas and his co-workers (10, 13).

Normal rabbits were given spaced (8 hours) intravenous doses of endotoxin and endotoxin and dextran following the schedule shown in Table I. From the table it is

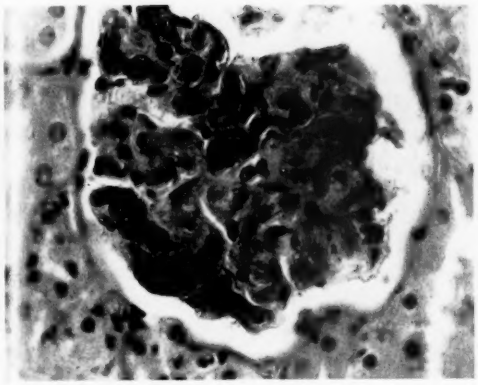

FIG. 3. Renal glomeruli showing homogenous eosinophilic material occluding terminal arterioles. Hematoxylin eosin stain, ×630.

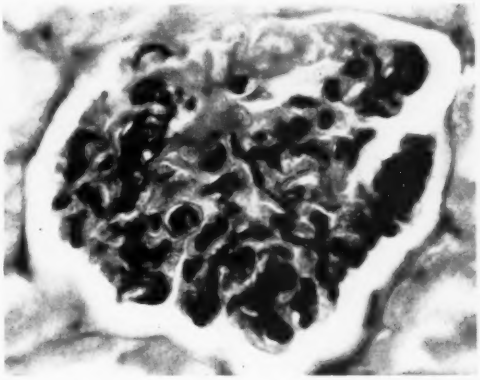

FIG. 4. Renal glomeruli showing occlusion of the terminal arterioles with homogenous eosinophilic material. Phosphotungstic acid hematoxylin stain, ×630.

apparent that neither endotoxin, 100 micrograms per 0.1 milliliter, nor dextran, 10 milligrams per 0.1 milliliter, singly affected the rabbits injected. However, two spaced injections of Serratia marcescens endotoxin, 100 micrograms, killed 2 rabbits in approximately 30 hours. Renal and lung lesions similar to those described by Thomas were evident in both animals. Similarly, an endotoxin injection of 100 micrograms followed in 30 minutes by 10 milligrams of dextran killed 1 of the 2 animals injected and this animal showed typical deposition of homogenous eosinophilic material in the glomeruli of the kidney. One animal did not die after this sequence of injections and when sacrificed demonstrated no renal pathologic changes.

An experiment was conducted to determine if human immune globulin, which reputedly contains high molecular weight polysaccharide as its antigenic fraction III, could evoke a typical Shwartzman reaction in a rabbit which had previously been sensitized with Serratia marcescens endotoxin. The animal so prepared demonstrated a small amount of necrosis locally which although minimal was certainly discernible from the control animal that had received the intradermal injection alone.

The role of endogenous polysaccharide was again demonstrated by the intravenous injection into a rabbit of 100 micrograms of crude burn diffusate. This material was obtained from a distilled water perfused air pocket (Selye pneumodermic technique) raised on the back of an adult white rat that had received a full-thickness burn. The rabbit previously sensitized with the Serratia endotoxin experienced necrosis of the skin in the region of the intradermal injection.

Properdin and lysozyme levels were run on the terminal serum of this patient as a means of measuring nonspecific host defense mechanisms. The properdin level as measured by the zymosan method was less than one. The normal level is 4 to 8 Pillemer units. The lysozyme level was found to be 2 micrograms per 0.25 milliliter. The normal level in the Surgical Research Unit laboratory is 3.

DISCUSSION

Individuals sustaining a thermal burn of 90 per cent of the body surface experience mortality in excess of 95 per cent. Death may occur within the first 72 hours due to profound physiologic alterations refractory to all presently known forms of resuscitation. In the few who survive beyond several days after this amount of trauma, death is expected within 20 days.

During the past few years coagulase-positive Staphylococcus aureus and Pseudomonas aeruginosa have been the organisms most frequently cultured from the peripheral blood prior to death in massively burned patients treated at this unit. Proteus and coliform organisms have been found less commonly. Serratia marcescens has never been found in burn wounds at the Surgical Research Unit and, to our knowledge, it has never been reported as a blood stream invader in thermal burns. The experience in the patient reported here suggests a possible real danger in using Serratia marcescens as a tracer organism in cloud chamber studies involving human beings and for the charting of retrograde bacilluria in patients undergoing urinary tract instrumentation.

Studies by Thomas, Good, and Brunson and others in the past 10 years have documented the typical response of the rabbit and the rat to injections of endotoxin and the influence of other substances on this response. The source of endotoxin used by these investigators was most frequently cultures of Serratia marcescens. More recently, the deposition of eosinophilic staining fibrinoid material in the glomerular tufts of human beings has been reported and incriminated in the cause of death.

In the present case, laboratory evidence documents the fact that the patient did have a Serratia marcescens infection involving, first, the surface wounds and the genitourinary tract, and, later, the blood stream. Any one of these foci could have produced the endotoxin necessary for either the sensitizing or the provoking dose. Bacterial agglutinins and hemagglutinins were of sufficient titer to indicate an active infection that concomitantly could have sensitized the host. The lesion found in the kidneys of the patient was identical to the lesions found in the laboratory animals after intravenous injection of endotoxin as established by special staining technique. In order to produce the lesion in lower animals prescribed intervals of time are necessary, so the precise mechanism of production of the lesion in this patient cannot be ascertained. However, if we assume that the previously mentioned laboratory work in animals can be transposed to man, the following mechanisms must be considered.

1. Endotoxin sensitization (bacterial or endogenous).—It can be postulated that the patient absorbed Serratia endotoxin from the large burned surface where bacteria were growing, the urinary bladder, or the blood stream to achieve preparatory sensitization of his organs. The evoking agent of the Shwartzman reaction in this patient then could have been endogenous polysaccharide (considered more fully *vide supra*) released by burned mammalian cells or more Serratia endotoxin from any of the sites mentioned. It is possible that sensitization and evocation occurred in a reverse sequence from these. In this connection, the use of shock plasma studies might have elucidated the roles of these factors. Only 2 to 3 milliliters of the patient's plasma were available, however, from the autopsy, and since almost a liter of plasma is required for this procedure, it was not performed.

2. Reticuloendothelial system blockage.—Several agents are known to block the reticuloendothelial system (thorotrast, trypan blue, and saccharate of iron iodine) (Table II) and, when followed by an intravenous injection of Serratia marcescens endotoxin, produce a generalized Shwartzman reaction. We might postulate that one of several substances administered to the patient could have blocked the reticuloendothelial system making him vulnerable to a generalized Shwartzman reaction after the entrance of endotoxin into the blood stream. This is not likely, however, since the substances administered intravenously were penicillin, streptomycin, whole blood, serum albumin, glucose in water, lactate Ringer's solution, demerol, normal saline, and immune globulin. The fate of the latter is unknown but it is possible that the high molecular weight polysaccharide contained in fraction III of this preparation might serve

is a reticuloendothelial system blocking agent.

3. Steroids.—It has been shown by Thomas and Good (12) that in rabbits treated for several days with cortisone a generalized Shwartzman reaction developed following the injection of a nonlethal dose of endotoxin. This patient in all probability sustained an injury which produced maximum stress and maximum steroid liberation. This may have set the stage for the generalized Shwartzman-type reaction which followed the entrance of Serratia marcescens into the blood stream. It is not believed, however, that the dose of 400 milligrams of cortisone given several hours prior to death as a desperation measure could have caused or influenced the reaction which apparently had been developing for 24 hours.

4. Heparin-like anticoagulants.—The patient received no heparin-like anticoagulant substances (dextran sulfate, sodium polyanethol sulfonate, or sodium polyvinyl alcohol sulfonate) which have been shown to produce the generalized Shwartzman reaction if injected intravenously after the preparatory endotoxin.

5. Radiation.—Large doses of x-radiation over the abdomen followed by nonlethal doses of endotoxin have produced generalized Shwartzman reactions in the rabbit. This patient's only exposure to x-ray was a minimal dose which had been required in order to take a single posteroanterior view of the chest.

6. Endotoxemia from burn wound.—The observation that crude burn diffusate given intravenously can produce a local Shwartzman reaction after an intradermal injection of Serratia endotoxin indicates that the diffusate might contain either an endotoxin or an anticoagulant substance which is heparin-like. It is possible then that if a generalized sensitivity had been present in the patient due to the endotoxin of the gram-negative organism on the surface, in the genitourinary tract, and in the blood, the absorption of the burn diffusate from the extensive eschar of the burned patient might represent the provoking dose of the generalized Shwartzman reaction.

TABLE II.—SOME KNOWN CAUSES OF THE GENERALIZED SHWARTZMAN REACTION

Evoking mechanism	*R.E.S. block*	*Provoking mechanism*	*Reaction*	*Bibliography ref. No*
Endotoxin I.V.	?	Endotoxin I.V.	+*	10, 13
Thorotrast I.V.	+	Endotoxin I.V.	+	4
Endotoxin I.V.	+	Thorotrast I.V.	—	4
Trypan blue	+	Endotoxin	+	4
Endotoxin I.V.	?	Trypan blue I.V.	—	4
Cortisone	?	Endotoxin I.V.	+*	12
ACTH	?	Endotoxin I.V.	+	12
Cortisone	?	Endotoxin I.D.	+	12
Gr. A streptococcus infection	?	Endotoxin I.V.	+	11
Gr. A streptococcus infection (timing)	?	Endotoxin I.V.	+ New lesion in myocardium	11
Colloidal carbon	+	Endotoxin I.V.	+	9
Saccharate of iron oxide	+	Endotoxin I.V.	+	9
Endotoxin I.V.	?	Dextran sulfate I.V.	+†	10, 13
Endotoxin I.V.	?	Na polyanethol sulfonate	+†	10, 13
Endotoxin I.V.	?	Na polyvinyl alcohol sulfonate	+	10, 13
Abdominal radiation	+	Endotoxin	+	6

*Prevented by nitrogen mustard.
†Prevented by heparin.

Any interpretation of the absence of serum properdin and the unelevated lysozyme level is also speculative. The massive release of endogenous polysaccharide from the thermally traumatized tissue, however, might have conjugated properdin as zymosan does and made it unmeasurable. The expected rise in lysozyme due to endotoxin damage of leucocytes probably did not materialize because of the leucopenia. The elevation of the serum nonprotein nitrogen terminally is consistent with the usual lesion and urinary output. The profound terminal leucopenia (1,200) is also consistent with the lower animal findings of Thomas and Good (12, 13).

SUMMARY

1. The clinical course, postmortem findings, and immunologic aspects of a patient who sustained severe burns followed by Serratia marcescens septicemia and a generalized Shwartzman reaction have been presented.

2. In this case it is postulated that a combination of stress produced by severe trauma followed by the presence of an endotoxemia due to Serratia marcescens in the wounds, in the genitourinary tract, and in the blood stream of this patient caused the generalized Shwartzman reaction.

3. In support of this thesis is experimental work performed in rabbits which demonstrated that preparatory intradermal sensitization by the patient's Serratia endotoxin followed by an evoking intravenous dose of burned rat diffusate or immune globulin could cause a local reaction. Other known mechanisms of production of the Shwartzman reaction have been reviewed and discussed.

4. In view of our findings, it is suggested that Serratia marcescens, a reputed nonpathogen, should be seriously regarded as a potential bacteremic agent in burn trauma, and the wisdom of its use as a tracer organism in human studies is challenged.

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EXPERIMENTAL PRODUCTION OF ESOPHAGEAL VARICES IN THE MACACA RHESUS

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THE EXPERIMENTAL PRODUCTION of ascites with temporary portal hypertension has been achieved by several means in a variety of animals. However, esophageal varices comparable to those seen in human beings have not been produced consistently in animals. Rousselot and Thompson injected silicone particles into the splenic vein of dogs but were unable to create full-blown varices. Baronofsky and Wangensteen gradually occluded the portal and splenic veins of dogs and obtained varices which could be made to bleed after the administration of a histamine-beeswax preparation. Morris and Miller, however, were not able to cause segmental venous hypertension nor esophageal varices in dogs with a somewhat similar technique.

We have observed that dogs with band-induced portal congestion occasionally exhibit esophageal varices if the ascites lasts for many months, but such varices are usually meager and do not bulge into the lumen. Recently, Tamiya and Thal produced large esophageal varices in the dog by a complex two stage operation, the first stage consisting of removal of potential collateral venous circulation by resection of the spleen, omentum, and tail of the pancreas, and the creation of an arteriovenous shunt between the left gastric vein and splenic artery. At the second stage operation, the splenic vein was partially occluded until the pressure in the cardiac veins reached between 40 and 50 centimeters of saline. This procedure has the disadvantage of a 50 per cent failure rate due to closure of the arteriovenous shunt. It appears from this work that in the dog, at least under the conditions of the experiment, arterial pressure is necessary in the portal collateral venous system for the formation of large esophageal varices.

We are reporting a method of producing experimental esophageal varices in the Macaca rhesus monkey by ligation maneuvers with veins only. The method is simple and reproducible. The technique consists of adapting a combination of venous ligation procedures previously described by other investigators. McKee and associates demonstrated that partial occlusion of the supradiaphragmatic vena cava of the dog almost invariably resulted in temporary ascites and portal hypertension. Child (3) found that monkeys and human beings could usually tolerate complete, sudden occlusion of the portal vein with little or no ill effect, in contrast with the invariable lethal outcome of this maneuver in dogs. We employed a combination of these procedures together with azygos vein ligation in a two stage operation in monkeys. Although our original purpose was to study the course of altered venous pressure relationships, we are reporting the method as well as some of our observations over a 5 year period because of the possible usefulness of the preparation to other investigators.

METHODS

Fourteen Macaca rhesus monkeys were processed through the Department of Animal Care and were declared free of disease after appropriate inoculations. The stand-

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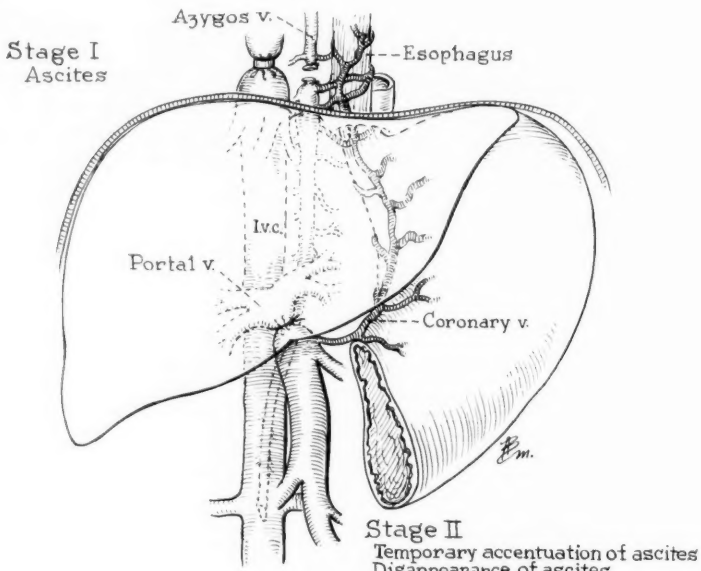

FIG. 1. Diagram of ligation maneuvers and their effects. First stage: 50 per cent constriction of supradiaphragmatic inferior vena cava and severance of azygos vein. Second stage: complete ligation of portal vein.

ard daily diet of stock monkey ration[1] was considered optimal in all nutrients and maintained a constant level of protein and sodium intake, except when altered deliberately.

All surgical procedures were performed under intravenous nembutal anesthesia, and a positive pressure automatic respirator was employed for intrathoracic procedures.

Preliminary experiments. The first 4 monkeys were subjected to 50 per cent occlusion of the supradiaphragmatic vena cava by placement of an aluminum band about the vessel in a manner similar to that used by McKee and associates in dogs. In contrast to the massive ascites seen in dogs 2 to 4 weeks after this maneuver, no discernible effect was seen in the monkeys. Six to 8 weeks later, the right thoracic cavity was re-entered. The azygos vein was found to be markedly distended in each instance. On the assumption that the azygos vein was serving as an adequate collateral channel for the constricted vena cava and thereby was preventing the formation of ascites, it was decided to ligate doubly and sever the azygos vein. In each of these 4 monkeys, ascites began to develop within a week after azygos vein ligation and progressed rapidly. Within 6 weeks, the abdomen measured 3 to 4 times its original girth. Subcutaneous veins in the abdominal wall became distended and tortuous.

Final experiments. As it was found that ligation of the azygos vein was a necessary adjunct to vena caval constriction for the production of ascites in monkeys, a second group of 4 monkeys was subjected to both procedures simultaneously. In all these animals massive ascites developed within 4 to 6 weeks. The lower extremities of the ascitic monkeys exhibited varying amounts of

[1]Rockland pellets, 50 grams (pellets contain ground whole wheat, cereal food crumbs, feeding oatmeal, soybean oil meal, fish meal, dried whole milk, dehydrated alfalfa meal, irradiated brewers' type yeast, 1% salt, 1% bone meal, dextrose); sunflower seeds, 10 grams; dried milk, 35 grams; ½ banana; ½ orange; ½ apple; 1 sliced carrot, and 2 or 3 lettuce leaves.

edema. In some, the edema diminished after several weeks. In others, it became chronic and woody, causing interference with motion. In 2 monkeys, a contracture of the knees developed after several months.

For periods ranging from 6 to 20 weeks, the ascites in the 8 monkeys with caval-azygos procedures remained relatively unchanged, except for slight cyclic variations occurring at 5 to 7 day intervals. With no change in diet, the ascites, once fully developed, appeared to wane for a day or two, then wax again for about 5 days, then wane again. We have no explanation for this cyclic phenomenon, but in previous work we observed a similar pattern in ascitic dogs (5).

In view of the known tolerance of monkeys to portal vein ligation, it was decided to subject the ascitic monkeys to sudden, complete ligation of the portal vein and to observe the effects of this maneuver. Previous work with dogs and with working models (4) indicated to us that portal vein constriction in ascitic animals may prevent the reaccumulation of ascitic fluid, under certain circumstances.

Six of the 8 ascitic monkeys were subjected to complete, sudden portal vein ligation 60 to 90 days after the vena cava-azygos vein procedure. The remaining 2 monkeys were kept for long-term observation without further surgery. At laparotomy, the aspirated ascitic fluid measured from 300 to 1,200 cubic centimeters. The portal vein was exposed, and its pressure, as measured by direct manometry, ranged from 38 to 60 centimeters of saline. (Control levels, obtained on a later group of monkeys, ranged from 9 to 17 centimeters of saline.) After ligation, portal vein pressures were again taken above, as well as below, the ligatures. On the hepatic side of the ligature, the pressure rapidly dropped after occlusion, but in no instance did it reach normal range. The lowest pressure above the ligature was 28 centimeters of saline. Below the ligature, portal vein pressures rose from 6 to 14 centimeters of saline above the already elevated levels. The fact that pressures above the ligature did not drop to normal levels would tend to confirm the role of the portal vein as a secondary outflow tract in the presence of elevated portal pressure.

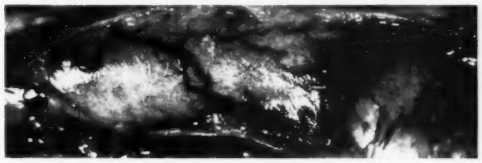

FIG. 2. Close-up view of esophageal varices at esophagogastric junction, as seen from the outside, after incising and separating muscular coat of esophagus.

In the period following ligation of the portal vein in monkeys with pre-existing portal hypertension, ascites rapidly reaccumulated for a period of 10 days to 2 weeks, at which time it began to diminish. As the ascites gradually lessened, the veins on the anterior abdominal wall actually became more prominent. Ten weeks after portal vein ligation, the girth of the abdomen returned almost to normal. At this time, 1 of the 6 monkeys died, apparently from pneumonia, and it was subjected to autopsy examination. A large network of veins was found about the liver, especially in the hepatoduodenal ligament and mesentery of the lesser curvature of the stomach. Upon opening the thoracic cavity, many tortuous veins were seen in the posterior mediastinum connecting enlarged esophageal veins with the vena cava, azygos, and hemiazygos veins.

Because of these findings, the remaining 5 animals were subjected to esophagoscopic examination by means of an infant esophagoscope at monthly intervals in order to observe the possible development of esophageal varices. In 4 animals, prominent esophageal veins were seen in the lower third of the esophagus. In the remaining animal, no esophageal veins were observed.

After 24 months, one of the monkeys with, and the one without, visible esophageal veins were sacrificed by performing a laparotomy and injecting the portal vein above

FIG. 3. Appearance of varicose plexus viewed from mucosal side.

and below the tie with a mixture of formalin and blue-black ink. Autopsy examination revealed tortuous, enlarged esophageal veins with large connecting veins between the portal and caval systems in 1 of the 2 monkeys (Figs. 2 and 3).

Ligations in reverse order. Performance of the ligations in reverse order, that is, portal vein ligation, followed some weeks later by thoracic vena cava constriction and azygos vein ligation, was carried out in 5 additional monkeys. By doing the abdominal phase of the operations first, it was possible to obtain control readings of portal pressures before they became elevated by constriction of the vena cava and azygos vein. However, in none of these 5 animals could esophageal varices be produced, despite additional ligatures of other veins (gastric, splenic, and hemiazygos) at various times.

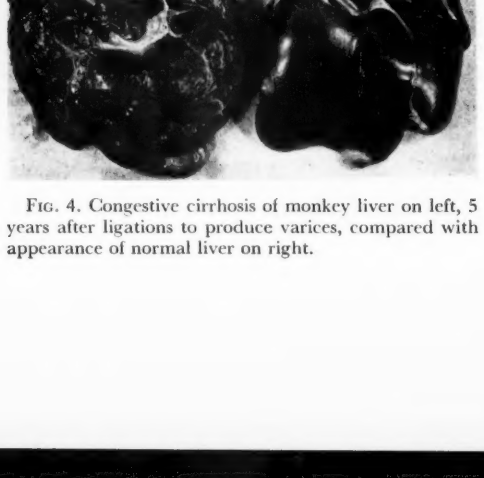

FIG. 4. Congestive cirrhosis of monkey liver on left, 5 years after ligations to produce varices, compared with appearance of normal liver on right.

Immediately after portal vein ligation in these monkeys, engorgement of abdominal viscera, previously described by Child (2) in the Macaca mulatta monkey, was also observed by us. This consisted of distention of the veins of the stomach and intestine and engorgement of the spleen. One of the monkeys in this group was found dead the morning after portal vein ligation. The other monkeys did not exhibit demonstrable ascites.

Two monkeys with ligations in reverse order were subjected to injection studies after 90 days of observation. These studies revealed a large number of collateral veins about the liver area and in the stomach wall after the portal vein ligation, apparently sufficient to channel off any increase in intrahepatic pressure induced by the delayed constriction of the thoracic inferior vena cava and ligation of the azygos vein. In neither of the 2 surviving animals in this group was the portal pressure found elevated 90 days after the ligations. The only observable residual lesion was lymphedema of the lower extremities with some limitation of motion in the knee joints.

Simultaneous performance of ligations. In 1 additional monkey, an attempt was made to perform all the ligations (caval constriction, azygos ligation, portal ligation) at one sitting. This resulted in death of the animal within 24 hours, apparently due to shock.

Some late observations. The course of the 6 animals with esophageal varices was followed for periods up to 5 years during which time periodic esophagoscopies, portal pressure determinations, liver biopsies, and blood chemistry studies were carried out.

Portal pressure observations at 60 to 180 day intervals indicated that somewhat elevated levels were maintained for periods up to 1 year, although they began to diminish after 90 days. After about 1 year, pressures approached normalcy, although the

varices persisted unabated throughout the 5 year observation period.

Study of liver morphology revealed that, as time progressed, the liver showed more and more evidence of congestive cirrhosis. After 5 years, the liver had the appearance shown in Figure 4. Similar changes were observed as early as 2 years after surgery. Microscopically, the sections revealed multiple venovenous and arteriovenous shunts (Fig. 5).

Except for a temporary diminution in total proteins and a slight rise in serum sodium during the period of ascites, no significant alterations in blood chemistries were noted. Excretion studies were not carried out. Additional observations will be reported separately.

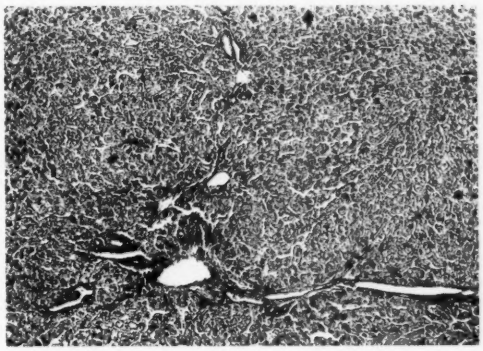

FIG. 5. Microscopic appearance of congestive cirrhosis of monkey liver showing shunts between portal and hepatic venous channels.

DISCUSSION

The technique described is a simple means of producing esophageal varices in the monkey.

At the time the ascitic monkeys were subjected to portal vein ligation, it was theoretically considered as a maneuver for the prevention of reaccumulation of the fluid. However, the rapid but temporary reaccumulation to an extent even exceeding that of preligation levels indicated that portal vein ligation actually blocked one of the auxiliary outflow tracts of the liver. This concept was supported by elevated pressure readings on the hepatic side of the tie immediately after portal vein ligation.

Spontaneous resorption of the reaccumulated ascitic fluid began about 6 weeks after the second operation (portal vein ligation) and was usually complete in 5 months, except for small cyclic reaccumulations.

It was of some interest that elevated portal pressures invariably returned almost to normotensive range within a year after the initial rise. However, long after the ascites disappeared, the varices persisted, and, in some instances, became progressively more prominent over a 5 year period. The question as to whether or not portal hypertension persists for long periods of time appears to depend on the balance between the degree of obstruction to the venous outflow tracts (hepatic veins and portal vein) and the adequacy of the collateral channels. As long as the former is greater than the latter, the portal pressure remains high. After sufficient collaterals develop, the monkey's portal pressure returns to normal, but the collateral channels, including the varices, remain prominent for as long as 5 years.

From our observations, it appears that: (1) when the venous occlusion is above the liver (vena cava, hepatic veins), ascites is the predominant result; (2) when the occlusion is at or near the porta hepatis, the portal hypertension is transient and leads to neither ascites nor esophageal varices; (3) when there is interference with hepatic vein outflow followed by interference with portal vein flow, ascites is temporarily accentuated, and a greatly increased pressure is transmitted through the coronary vein and other collaterals, leading to esophageal varices as the predominant lesion.

If the caval-azygos ligations above the liver can be likened, in effect, to postsinusoidal obstruction in the cirrhotic liver, and the portal vein ligation to presinusoidal obstruction, our observations may be of some value in the search for an explanation as to why ascites alone is seen in some cirrhotic patients, ascites and varices in others, and varices alone in still others.

SUMMARY

An easily reproducible preparation is described which appears to provide a convenient means of studying the natural history of portal hypertension, ascites, esophageal varices, and congestive cirrhosis in the Macaca rhesus monkey.

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THE DOUBLE PORTACAVAL SHUNT IN THE TREATMENT OF CIRRHOTIC ASCITES

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THE MECHANISMS involved in the formation of ascites by patients with liver disease are complex but the available information suggests that intrahepatic obstruction in the vascular bed, referred to in this report as the "outflow block" phenomenon, plays an important role in the pathogenesis of cirrhotic ascites. It is on this basis that surgical decompression of both the splanchnic and hepatic vascular beds has been used in patients with intractable ascites.

In a preliminary report on the surgical treatment of cirrhotic ascites, the experimental, clinical, and morphologic evidence supporting the concept of an intrahepatic "outflow block" as the initiating factor in the multiple physiologic and endocrinologic abnormalities associated with the accumulation of ascitic fluid in patients with liver disease has been reviewed (6), but a few of the significant facts and observations will be mentioned again. Ascitic fluid has approximately the same composition as liver lymph; experimental ascites is consistently produced by outflow occlusion, and transudation from the liver accounts for a major portion of the accumulated fluid; portal vein occlusion, experimental or clinical, rarely if ever results in the formation of any appreciable amount of ascitic fluid, and data in this report demonstrate that intrahepatic portal pressure does not fall appreciably even after diversion or occlusion of the splanchnic inflow. Herrick showed by perfusion studies that elevated intrahepatic venous pressure was maintained by the arterial inflow in cirrhotic livers but not in normal livers, and the occasional effectiveness of hepatic arterial ligation in the treatment of ascites supports this concept of intrahepatic arterioportal communications.

In stressing the factor of the "outflow block" it is not our intention to negate the importance of decreased intravascular osmotic pressure, but this plays a relatively minor role, particularly in patients with serum albumin levels greater than 3 grams per cent.

The increased aldosterone secretion with tubular resorption of sodium, which sets up a vicious circle and presents difficulties in medical management, is a phenomenon secondary, in all probability, to the changes in plasma volume and in electrolyte distribution. The importance of this secondary hyperaldosteronism is emphasized by the effects of adrenotoxic drugs, of aldosterone inhibitors of antagonists, and of surgical ablation of the adrenal glands. Therapy pointed in this direction, however, is an attack on a secondary disorder and not on the primary physiologic derangement. In addition, the existence of cirrhotic ascites is frequently, although not invariably, associated with esophageal varices, and any procedure which does not reduce portal hypertension and portal hypervolemia leaves the patient under the threat of exsanguinating hemorrhage.

The long history of ingenious surgical attempts to divert or alter the accumulation of the protein-rich ascitic fluid from the peritoneal cavity has been in general disappointing, and the various surgical procedures have been attended by a high mortality.

When Whipple demonstrated the feasibility of shunts in man, it was hoped that

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these operations would be effective in controlling ascites as well as in preventing hemorrhage from esophageal varices. The results in general, however, proved to be disappointing and the mortality high in patients with intractable ascites although, in some instances, clinical improvement was gratifying.

In this hospital, the mortality in this group was reported by Linton (4) as 44 per cent in 1951, and Menendez and Linton have stated that "when ascites is refractory to conservative measures, a shunting procedure is not recommended. Contrary to some views, it is believed that ascites may be increased rather than decreased by the portacaval anastomosis" (7). Prior to the introduction of the procedure to be described in this report, in this hospital there were 22 patients with ascites and esophageal varices for whom other types of shunts had been constructed (either end-to-side portacaval or splenorenal). Six patients died with rapidly reaccumulating ascites in the postoperative period, a mortality of 27 per cent. Eight patients did well, and the remainder survived but ascites continued to accumulate. Interesting, and probably pertinent to the physiologic concepts expressed in the present report, is the fact that 7 of the 8 good results were in patients with splenorenal shunts, a procedure which accomplishes to some extent decompression of both the splanchnic and the hepatic vascular bed. It is also interesting that in some patients with end-to-side portacaval shunts constructed because of hemorrhage alone, ascites later developed which did not exist prior to operation. The fact that end-to-side portacaval shunt which achieves no hepatic decompression is sometimes followed by the dissipation of ascites may well be due to the diversion of a portion of the inflow volume, as suggested by the experimental studies of Hayano. A physiologic analogy may be drawn between this procedure and hepatic arterial ligation which has also been utilized in attempts to control intractable ascites.

The double shunt procedure to be described is based on the concept that an intrahepatic outflow block is the initiating factor in the complex derangement resulting in ascites, and that maximum decompression of both the splanchnic and hepatic vascular beds is essential for optimal correction of the disordered physiology.

MATERIAL AND METHODS

The 12 patients reported in this series do not represent a homogeneous group. The only common denominators were the presence of cirrhosis and the existence of intractable ascites. There was a wide range in the degree of what might be called "operative risk." The clinical status and the metabolic change following operation are summarized in Tables I and II, and Figure 1. Rather than report in detail all the liver function tests on each patient, a "liver index" was calculated according to a method defined in Table III. In general, operation was not advised until medical consultants had agreed that conservative measures had failed in controlling the accumulation of ascites; in several instances, however, the threat of recurrent hemorrhage from esophageal varices made early operation more imperative than it would have been had ascites alone been the problem.

In addition to standard liver function tests, the urinary sodium-potassium ratio was observed, liver blood flow and total blood volume were determined before and after operation, and the weight and girth observed and recorded.

Creatinine clearance was measured in some patients to determine to some extent whether or not the urinary sodium-potassium ratio was a reasonable index of aldosterone activity and as an indirect estimate of effective circulating blood volume.

Sodium and potassium measurements were done on the Baird flame photometer according to standard techniques.

Liver flow determinations were carried out as described by Nardi (8) based on the method of Dobson which utilizes the disap-

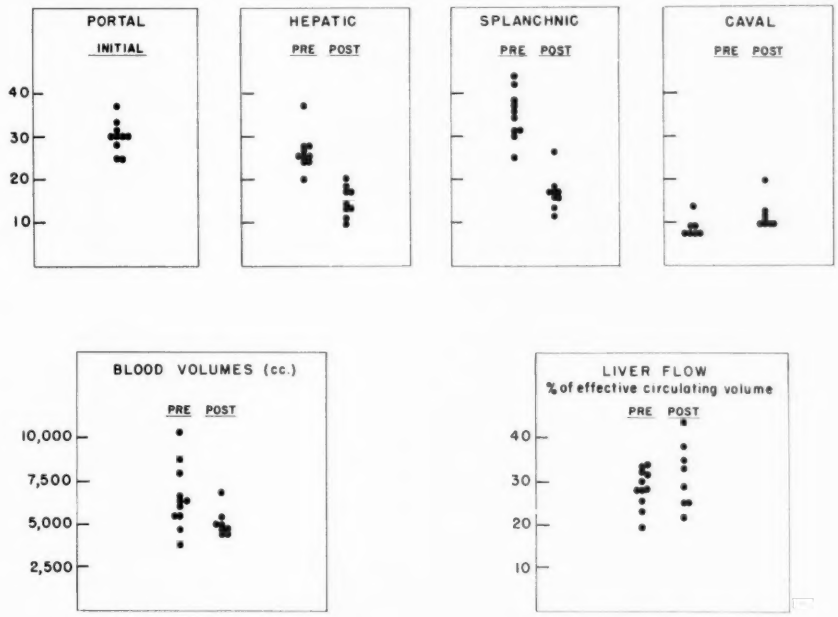


FIG. 1. Diagram of changes in portal pressures in centimeters of water, blood volume, and liver blood flow attendant upon operation.

pearance rate of P^{32} labelled chromic phosphate from the peripheral blood as an index of effective blood flow through the liver parenchyma. Because blood volume measurements, particularly in the patient with cirrhotic ascites, do not of necessity represent effective circulating blood volume, it is more accurate to report hepatic blood flow measured by clearance of a colloid, in terms of percentage of total clearance and compare this to the normal, rather than represent the data as indicating actual volume of blood cleared.

Blood volume determinations were done by the Evans blue dye technique; calculations were based on 10 minute measurements and within this interval no appreciable amount of the dye appeared in the ascitic fluid. On occasions, this technique was checked by simultaneous calculation based on the chromated red cell method; there was no apparent discrepancy in the data obtained by these different techniques. The results are recorded as measured total volumes rather than per unit of weight or of surface areas because of the presence of ascites in this group; height and both "wet" and "dry" weights are given when available so that the reader may recalculate these volumes in units of surface area or weight.

When possible, the balance studies were carried out on a metabolic ward under carefully controlled conditions. The studies shown graphically in Figures 3, 4, 5, and 6 were all obtained under these circumstances.

OPERATIVE TECHNIQUE

In all instances, operative exposure was obtained through an oblique right subcostal incision extending from the mid-rectus well out in the flank with the patient in a semithoracotomy position. Paracentesis was not done prior to operation, and ascitic fluid was removed by suction and measured at the time the peritoneum was opened. After adequate exposure and stripping of the portal vein and inferior vena cava, anastomoses were constructed either by the technique of

TABLE I.—CLINICAL STATUS OF PATIENTS

Case No. Name Age, yrs.	Microscopic diagnosis	Preoperative: Albumin, gm. per cent	Liver index	Varices: Degree	Varices: Bleeds	Ascites: Amount, liters	Ascites: Duration, mos.	Type of shunt	Postoperative: Albumin, gm. per cent	Liver index	Varices: Degree	Varices: Bleeds	Ascites, liters	Duration of follow-up	Outcome
1 F.DeM. 43	Portal cirrhosis postnecrotic	3.3	2.3	0	0	10	14	Double porta-caval	3.4	1.8	0	0	0	25 mos.	Excellent; overweight
2 K.S. 39	Portal cirrhosis postnecrotic	3.3	2.5	4+	2	14	8	Double porta-caval	3.6	1.7	0	0	0	14 mos.	Excellent; overweight
3 B.B. 61	Cholangio-litic biliary cirrhosis	2.9	2.8	3+	1	11	4	Side-to-side portacaval	2.9	2.8	0	0	0	13 mos.	Excellent
4 G.B. 56	Portal cirrhosis postnecrotic	2.9	2.5	1+	1	7	9	Double porta-caval	2.4	3.6		0	0	2 mos.	Immediate result good; died of coronary heart disease (2 mos. postop.)
5 P.M. 82	Portal cirrhosis Laennec's	2.9	1.2	0	0	18	9	Side-to-side portacaval	2.8	1.6	0	0	0	10 mos.	Excellent
6 M.C. 41	Portal cirrhosis Laennec's	3.3	1.9	0	0	15	9	Double porta-caval	4.0	1.2	0	0	0	10 mos.	Excellent (see Fig. 7)
7 F.C. 45	Portal cirrhosis postnecrotic	2.2	3.2	2+	1	10	10	Double porta-caval	2.9	3.8				12 days	Died in hepatic decompensation
8 A.B. 49	Portal cirrhosis Laennec's	3.6	2.0	4+	3	8	6	Double porta-caval	3.3	2.0		0	0	6 mos.	Excellent
9 M.W. 57	Portal cirrhosis Laennec's	2.6	2.9	3+	1	9	7	Double porta-caval						21 days	Died of peritonitis and hepatic decompensation
10 I.B. 53	Portal cirrhosis Laennec's	2.6	2.5	4+	1	6	8	Double porta-caval	2.9	2.1	0	0	0	5 mos.	Excellent
11 I.H. 68	Portal cirrhosis	3.0	1.1	3+	2	9	9	Double porta-caval	2.9	1.4	3+	2	9	4 mos.	Failure; shunt occluded on splenoportogram; S-R shunt planned
12 P.C. 57	Portal cirrhosis postnecrotic	2.5	2.5	4+	3	8	24	Double porta-caval	2.0	2.8	0	0	0	2 mos.	Excellent

P.C. 57	postnecrotic cirrhosis									porta-caval							

TABLE II.—SUMMARY OF PERTINENT METABOLIC DATA

Case No. Name	Venous pressures, cm. of water: Preshunt: Portal	Preshunt: Hepatic	Preshunt: Splanchnic	Preshunt: Caval	Postshunt: Portal	Postshunt: Hepatic	Postshunt: Splanchnic	Hepatic blood flow, per cent effective blood volume per minute: Caval	Hepatic blood flow: Preop.	Hepatic blood flow: Postop.	Blood (plasma) volume, ml.: Preop.	Blood (plasma) volume, ml.: Postop.	Weight (lbs.): With Ascites	Weight (lbs.): Dry	Height inches	Urinary Na/K ratio: Preop.	Urinary Na/K ratio: Postop.
1 F.DeM.	31	24	37			17	17		19	22	10,340 (6,000)	5,000 (2,545)	174	154	76	0.05	2.0
2 K.S.	25	25	25	8		11	11	11	33	29	8,100 (4,700)	5,400 (3,294)	149	118	63	0.03	1.4
3 B.B.					14								114	93	65	0.04	1.1
4 G.B.	30	24	30			18	18		32	25	6,100 (3,738)	4,615 (2,585)	121	107		0.03	
5 P.M.	25	20	42		13			12	23	35	4,763 (2,715)	4,925 (2,364)	179	145	59	0.02	1.3
6 M.C.	28	25	43	13		20	26	20	30	33	8,880 (5,780)	4,700 (3,243)	127	98	64	0.03	2.1
7 F.C.	37	37	38	9		17	17	14	28		3,810 (2,364)		142			0.05	
8 A.B.									25	38	6,550 (3,670)	4,846 (3,150)	180	153	68	0.5	1.8
9 M.W.	30	26	34	8		14	13	13	31		5,553 (3,443)					0.1	
10 I.B.	30	27	31	8		13	16	11	28	25	6,200 (3,600)	4,460 (2,675)	120	109	61	0.11	1.6
11 I.H.	30	27	31	8		13	16	11	35		5,526 (3,758)		104	87	60	0	0
12 P.C.	33	25	36	9		12	17	11	28	46	5,875 (3,490)	6,924 (4,778)	143	127	68		

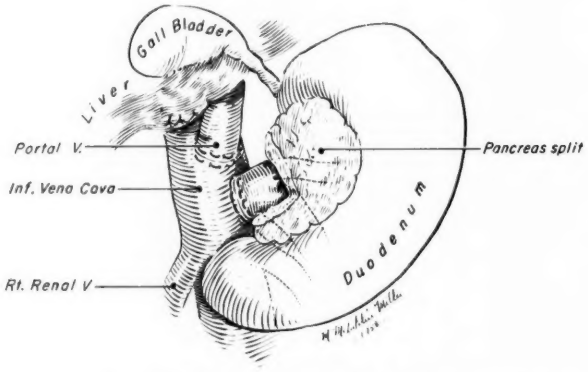


FIG. 2. Diagrammatic representation of the operative procedure referred to as the double shunt.

the double shunt, or, in 2 instances, by the more standardized side-to-side method.

The double shunt is constructed by dividing the portal vein about 4 centimeters from its bifurcation in the porta hepatis and anastomosing each end separately to the inferior vena cava. A continuous everting mattress suture—interrupted at three points—was employed. The hepatic end of the divided portal vein lies easily on the anterior wall of the vena cava while the splanchnic end lies more medially and inferiorly just above the left renal vein. In order to obtain adequate length and to avoid angulation, it is frequently necessary to split the pancreas and to resect a portion of the caudate lobe of the liver with its small hepatic vein; no untoward sequelae have attended these maneuvers.

TABLE III.—METHOD OF CALCULATING LIVER INDEX

Rating for liver index	*0*	*1*	*2*	*3*	*4*
Bromsulfalein per cent retention	<4	<10	<20	<30	>30
Albumin (gms. per cent)	>3.9	<4.0	<3.5	<3.0	<2.5
Vanden Bergh (mgms. per cent)	<1.0	<1.5	<3.0	<6.0	>5.9
Alkaline phosphatase (Bodansky units)	<4.0	<6.0	<15	<30	>29
Cephalin flocculation (48 hours)	0	1	2	3	4
Prothrombin time (per cent of normal)	>80	<80	<60	<40	<20

The appearance of the completed double portacaval shunt is shown diagrammatically in Figure 2.

RESULTS

Clinical results are summarized in Table I. Twelve patients had combined hepatic and splanchnic decompression, 2 by side-to-side portacaval shunts and the remainder by double end-to-side shunts. Two patients died postoperatively with hepatic decompensation; in each case the terminal events involved complete failure of the clotting mechanism. One patient (Case 4) has since died of a sudden arrhythmia during an episode of cardiac decompensation; ascites had been dissipated by the operation, however, and the late death seemed unrelated to the procedure. One patient (Case 11) was classified as a failure; postoperative splenoportogram demonstrated occlusion of the shunt, however, and the failure should be classified as a technical error; a splenorenal shunt is planned for this patient. The remaining 9 patients are living and well with no recurrence of ascites; no restriction of salt intake and no diuretics have been used since operation; the general improvement in all has been impressive with true body weight gain, return of menses in 2 premenopausal women, and a sense of well being in all. A photograph (Fig. 7) illustrates the dramatic

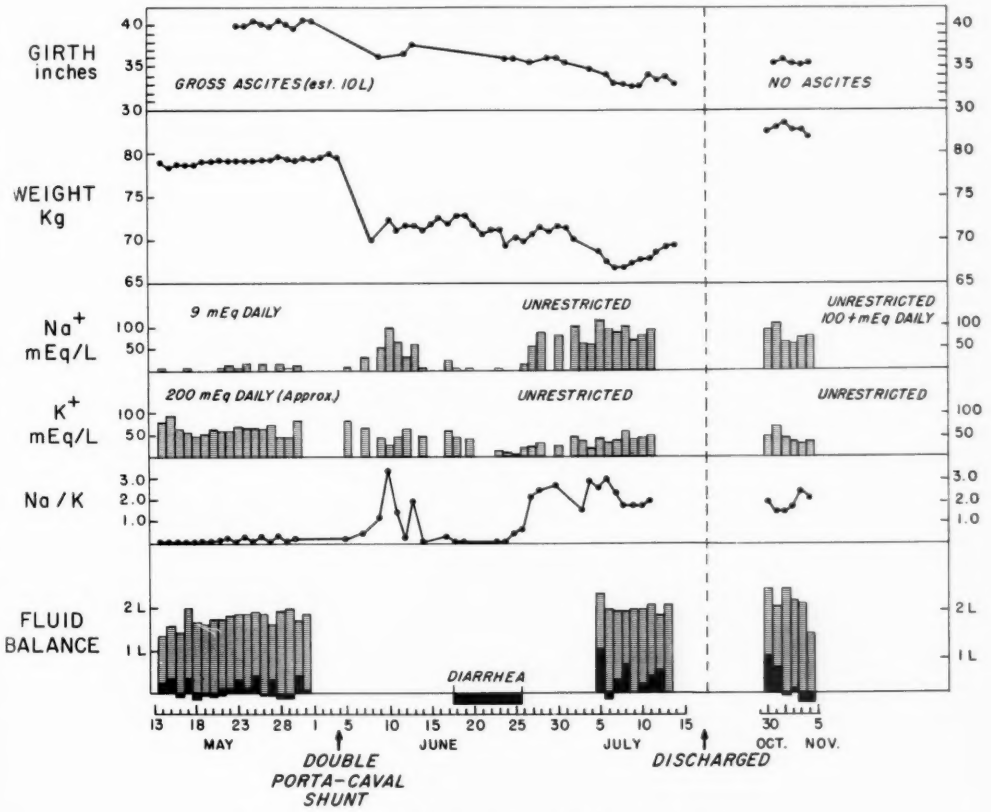


FIG. 3. Diagram of clinical and metabolic changes in Case 1.

change which can be expected within a few months after operation. In 5 of the survivors who had 1 or more hemorrhages in addition to ascites, varices have disappeared and there have been no further bleeding episodes. From the liver indices and albumin levels (Table I), there is no evidence that the operations resulted in a deterioration of liver function; in only 1 instance (Case 4) were these data worse than preoperatively, and, in this instance, measurements were obtained during what proved to be terminal congestive heart failure 2 months after initial discharge. The 2 operative deaths occurred in patients with advanced liver disease, liver indices of 2.9 or worse, serum albumin levels less than 2.6 grams per cent, and prothrombin times of less than 30 per cent; criticism could be made of the selection of these 2 patients for an operative procedure.

The results of pressure measurements, blood volume, and liver blood flow determination are summarized in diagrammatic form in Figure 1.

The measurements of portal pressure are interesting primarily in the relatively slight change which occurred in either the hepatic or splanchnic side of the occluded portal vein. There was an average fall of intrahepatic pressure of only 4 centimeters of water, and an average rise in splanchnic pressure of 5 centimeters of water after the main portal vein had been occluded or divided. In no instance did the hepatic pressure rise after portal vein occlusion so

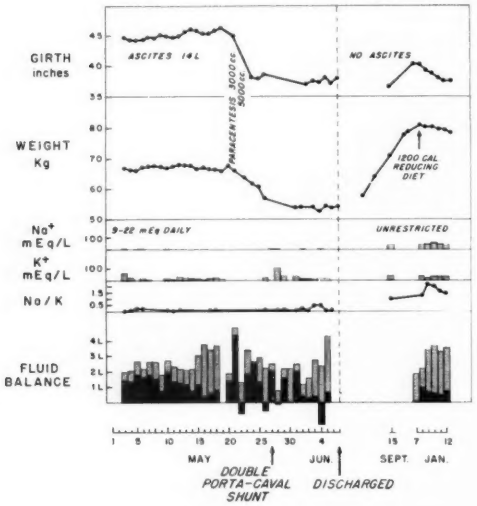


FIG. 4. Diagram of clinical and metabolic changes in Case 2.

that, in this series at least, the portal vein did not function as an outflow tract.

Measurement of hepatic blood flow gave a wide range (19 to 33 per cent) but the average (28 per cent) was less than the figure of 33 per cent reported by Nardi and Palazzi (9) for normal individuals. It is pertinent to note, however, that combined hepatic and splanchnic decompression caused relatively little change in effective blood flow to the liver (Table II, Fig. 1). Only 1 case (Case 4) showed a significant fall, and it is interesting that this occurred in the patient who died later after having recovered from the operation and the ascites; it would be premature to place any significance on this observation. In the other cases, there was either a rise in effective flow or no appreciable change.

Blood and plasma volumes were abnormally high and with 1 exception reverted to normal in the late postoperative period (Table II, Fig. 1). It was fully realized that any method involving albumin, whether isotopic or dye, is subject to the error of leakage from the intravascular compartment. For this reason, an equilibration time of only 10 minutes was used. This is adequate for mixing but little exchange between the intravascular and interstitial compartments occurs in this interval, and no dye could be detected in the ascitic fluid on the several occasions when this was measured. Blood volume determinations by the chromated red cell technique showed no discrepancies from the data obtained by the T-1824 dye technique.

Creatinine clearance determinations in 4 of these patients were all less than 100 liters per 24 hours, a distinctly subnormal clearance. This observation suggested that, despite an abnormally high total blood volume, this group of patients may have an actual decrease in the effective circulating volume.

The balance studies showed an invariable pattern of retention of sodium and abnormally high excretion of potassium (Table II, Figs. 3, 4, 5, and 6). This is consistent with other studies demonstrating this pattern of secondary hyperaldosteronism which makes the medical management of these patients so difficult. Postoperatively, this pattern was reviewed and the urinary sodium-potassium ratio returned to normal (Table II, Figs. 3, 4, 5, and 6). The appearance of an appreciable amount of sodium in the urine occurred as early as the eighth postoperative day (Case 1, Fig. 3) and, as might be expected, coincided with the final dissipation of the reaccumulated ascites. Typical metabolic and clinical patterns are shown diagrammatically (Figs. 3, 4, 5, and 6).

The problem in postoperative management should be considered briefly. In some of these patients ascites will reaccumulate rapidly in the immediate postoperative period, and it may be 1 to 3 weeks before sodium begins to appear in the urine and diuresis begins. During this period of rapid reaccumulation, it is imperative to maintain fluid and electrolyte balance and a normal plasma volume by appropriate replacement therapy. Inadequate replacement may well result in hypovolemia, hyponatremia, anuria, and death.

Four pertinent case histories are given in more detail.

CASE 1. F. D., a 43 year old man, was admitted to the hospital for study and treatment of ascites. For 10 years he had been a "moderately heavy drinker," taking a quart of wine or a pint of whiskey daily. Dietary intake was admitted to be adequate. About 1 year before admission he noticed an increase in abdominal girth and was admitted to another hospital, where he was told that he had liver disease and ascites. Since then, he had abstained from alcohol completely and followed treatment faithfully.

Despite abstention from alcohol, a good well balanced diet, a severely restricted salt intake (approximately 500 mgm. daily), and diuretics, the ascites persisted. A number of paracenteses were done, with only temporary relief.

On admission to this hospital the patient presented the findings of extreme accumulation of ascitic fluid. No esophageal varices were seen on x-ray examination. The pertinent laboratory findings were consistent with moderate impairment of hepatic function. It should be pointed out that, despite the ascites, the albumin level was well maintained at more than 3.0 grams per 100 milliliters.

A balance study was carried out in the metabolic ward, and the results are shown in Figure 3. Despite rigorous sodium restriction (200 mgm. daily), added potassium chloride, and treatment with mercurial diuretics, there was no change in weight or girth and no evidence of diuresis. The metabolic pattern was consistent with hyperaldosteronism and demonstrated almost total absence of sodium in the urine and excretion of potassium in large amounts.

On the twenty-third hospital day, exploration was carried out through a right lateral subcostal and flank incision. The findings were as expected, those of cirrhosis of the liver (postnecrotic type by microscopic examination) and portal hypertension. The portal pressure was equivalent to 31 centimeters of saline solution. After occlusion of the portal vein, the pressure on the intestinal side rose to 37 centimeters and that on the hepatic side fell to 24 centimeters of saline solution. Because the object of this operation was to achieve hepatic as well as portal decompression, a double end-to-side portacaval shunt was constructed. Postshunt pressure was recorded at 17 centimeters of saline solution.

Naturally, the ascites was dissipated by laparotomy, but the patient has never (the present follow-up period extends for more than 2 years) reaccumulated fluid within the peritoneal cavity, despite unrestricted salt intake and the absence of any specific treatment. He has had a vigorous appetite and has felt in excellent general health.

CASE 2. K. S., a 39 year old housewife with a history of chronic alcohol intake until 1 year before entry, was referred to the emergency ward of the Massachusetts General Hospital because of massive hemorrhage from esophageal varices. On admission she was in shock, showed the stigmas of liver disease and had tense ascites which had been intractable to medical management in the 8 months preceding admission. She lapsed rapidly into coma, but within 48 hours showed considerable improvement on a program of balloon tamponade, cathartics, enemas, neomycin, transfusions, and parenteral glutamic acid and arginine. Steady improvement continued despite 1 further hemorrhage but there was no diuresis or change in the tense ascites despite rigorous salt restriction, chlorthiazide, and mercurials.

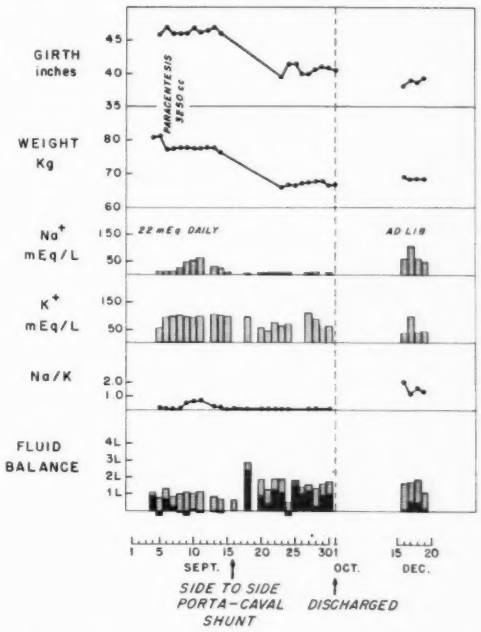


FIG. 5. Diagram of clinical and metabolic changes in Case 5.

Eight weeks after admission a double portacaval shunt was carried out. Preoperative and postoperative clinical and metabolic data are shown in Tables I and II and in Figure 4. She was discharged on the twelfth postoperative day after an uneventful convalescence. There was a transient reaccumulation of ascites which disappeared prior to discharge.

During the succeeding 8 months, she gained 54 pounds in weight and caloric intake was restricted to 1,200 calories daily to prevent excessive obesity. Fourteen months postoperatively, she is in excellent general health, is not restricted on salt intake, takes no medication, has had a restoration of a normal menstrual cycle after 3 years of amenorrhea, and has had no ascites at any time.

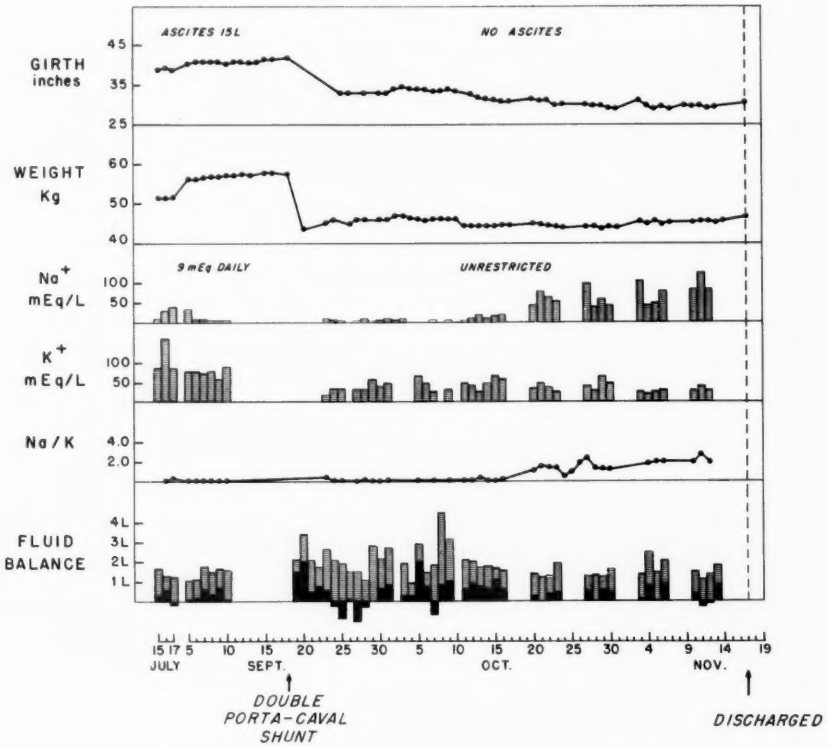


FIG. 6. Diagram of clinical and metabolic changes in Case 6.

CASE 5. P. M., an 82 year old Italian-born widow, was admitted because of intractable ascites of 9 months' duration. Stigmas and abnormal laboratory tests of chronic liver disease were present. There was a history of a moderate steady intake of wine. The picture was complicated by the fact that mild congestive heart failure had required full digitalization some months before, and by the fact that the patient would not eat when placed on a restricted (200 mgm. daily) salt intake. For 6 months, it had been necessary to carry out paracenteses which averaged 15 liters at intervals of 2 weeks.

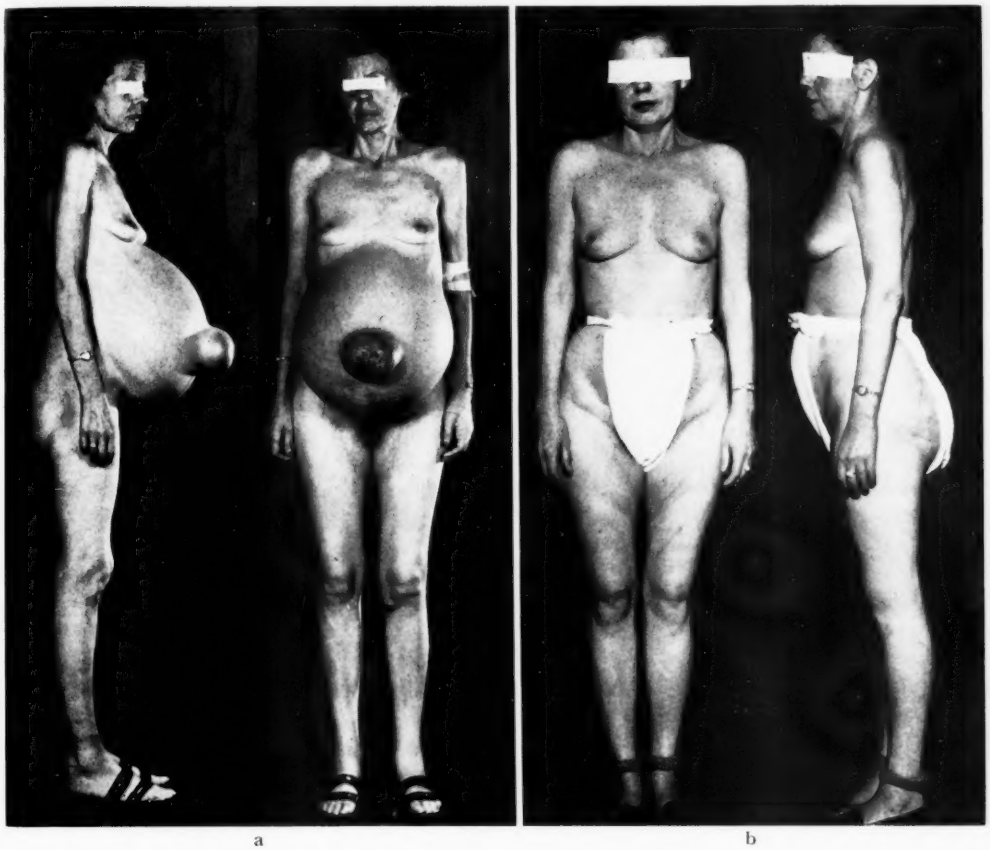
On the thirteenth hospital day, a side-to-side portacaval shunt was constructed. Convalescence was uneventful and the patient was discharged on the sixteenth postoperative day. Ten months after discharge, she was in good general health and there was no reaccumulation of ascites although moderate ankle edema persisted.

She was readmitted to the metabolic ward for a brief period of study 3 months after operation. Pertinent clinical and metabolic data are given in Tables I and II and Figure 5.

CASE 6. M. C., a 40 year old female separated from her husband, was a known alcoholic of many years' duration but had allegedly stopped drinking 4 years ago. Diagnosis of cirrhosis was made 6 months prior to the present admission. She was finally admitted to the hospital because a vigorous program of medical management on an ambulatory basis had failed to affect the ascites. Over the ensuing months, multiple combinations of treatment had been used with only very transient periods of minor diureses. Liver function was good, however, and at the end of a period of 3 months, the patient was transferred to the surgical service and a double portacaval shunt operation was performed.

There was an immediate reaccumulation of ascites but by the end of the third week, sodium began to appear in the urine in increasing amounts and the ascites was rapidly dissipated. Nine months postoperatively, she is in excellent health, has no ascites, and has gained 30 pounds of true body weight. The dramatic improvement can be visualized in the photographs of this patient which are reproduced in Figure 7.

Clinical and metabolic data are given in Tables I and II and Figure 6.



a b

FIG. 7. Photographs in Case 6: a, preoperative; b, 5 months after double shunt.

DISCUSSION

The accumulation of ascites in patients with cirrhosis of the liver is primarily a medical problem and in most instances the dissipation of the peritoneal fluid can be accomplished by rigorous restriction of salt intake and adjuvant measures. A number of patients, however, are refractory to medical management, and still others present, with the other serious problem of portal hypertension, bleeding esophageal varices. It is these two groups of patients with cirrhotic ascites for which surgery should be seriously considered.

Based on the concept that a postsinusoidal intrahepatic block is a major factor in the complex metabolic and hemodynamic derangements associated with the formation of cirrhotic ascites, an operation (double portacaval shunt) has been devised with the objective of achieving maximal decompression of both the splanchnic and intrahepatic vascular beds. Interruption of a portion of the inflow by hepatic arterial ligation or by single end-to-side portacaval shunt has been to some extent successful in controlling ascites. The mortality of arterial ligation has been high, however, and the procedure has met with serious objections. End-to-side portacaval shunt has been occasionally, but not universally, successful in the control of ascites and in our experience this procedure

has been sometimes followed by the accumulation of previously nonexistent fluid. Successful shunting procedures have been reported which involve both hepatic and splanchnic decompression. There are obvious objections, however, to the use of a venous T-graft as suggested by Theron and Allan. Although initial results were good, they recognized the shortcomings of a venous graft, and it seems likely that thrombosis would occur in a high proportion of cases. A satisfactory splenorenal shunt will to some extent decompress both the vascular beds but in our experience has been attended by a number of failures.

The side-to-side portacaval shunt as employed by Welch in ascitic patients has been successful and is theoretically sound. In the past, objections have been raised to the use of a side-to-side shunt on the grounds that the slitlike orifice which results if there is any tension on the anastomosis is prone to thrombotic occlusion. In theory, to achieve the same degree of splanchnic and hepatic decompression as the double end-to-side shunt, the total surface area of the constructed stoma should be equal to twice that of the portal vein itself. Longmire has shown that a side-to-side shunt does not invariably effect complete diversion of the splanchnic inflow, and therefore maximal decompression of the intrahepatic vascular bed is not achieved. In practice, however, there may prove to be little or no difference in the clinical results achieved by either procedure. Certainly, the 2 patients in this series treated by side-to-side shunts (Cases 3 and 5) had eminently satisfactory results.

Other diversion procedures such as ileal entectropy do not alter the basic problem of portal hypertension, and patients with esophageal varices continue to live under the threat of exsanguinating hemorrhage. In fact, 3 out of 10 patients bled massively from varices during the immediate postoperative period.

The metabolic and physiologic disorders in patients with cirrhotic ascites are difficult to untangle. The hyperaldosteronism, which is so rapidly reversed by a successful operation, is probably secondary to changes either in osmolarity or in volume. The elevated blood and plasma volumes in this and other series of cirrhotic ascites seems incompatible with the latter possibility. However, the elevated total blood volume is not, of necessity, correlated with the effective circulating volume and it may well be that abnormal compartmentation results in an actual hypovolemia in a constricted arterial bed. The depressed creatinine clearance values would support this possibility. Further studies on the factors controlling aldosterone secretion under these circumstances are in progress. A more searching analysis that is pertinent to this report has been given by Nardi (9) of the factors involved in the measurement of hepatic blood flow by the clearance of radioactive chromic phosphate. It is apparent from the data (Table II, Fig. 1) that there is no consistent decrease in blood flow to the liver as measured by this technique despite diversion of a large volume from both the hepatic and splanchnic vascular beds. In fact in the majority of cases the flow was unchanged or showed an increase after operation. Presumably this must indicate a compensatory increase in the effective volume of blood reaching the hepatic parenchyma through the hepatic arterial tree.

The pressures recorded at operation were interesting primarily in that occlusion of the portal vein caused so little change in either the splanchnic or hepatic pressures. Although there was a slight average increase on the splanchnic side and decrease on the hepatic side, these changes were minimal (Table II, Fig. 1). This would imply that the intrahepatic portal bed pressure is supported by an inflow system other than the splanchnic bed. The high oxygen saturation of this blood (up to 93 per cent) lends weight to the concept of arteriovenous shunts between the hepatic arterial inflow and the intrahepatic portal bed. In addition, these observations support the thesis on which hepatic decompression is suggested, of a postsinusoidal outflow block.

Regardless of the theoretic implications of some of the studies, it seems clear that shunt surgery of a type which will afford satisfactory decompression of both the hepatic and splanchnic vascular beds can reverse the clinical picture of the thin, wasted, chronically ill, ascitic patient and will restore the abnormal metabolic and endocrinologic pattern to normal.

SUMMARY

1. Twelve cases of cirrhotic ascites have been treated surgically with combined splanchnic and hepatic decompression. There were 2 postoperative deaths. In 9 of the 10 survivors, ascites has been dissipated rapidly without the need for salt restriction or diuretic agents. One case is classified as a failure because of occlusion of the shunt; splenorenal anastomosis is planned.

2. Studies on portal pressure measurements, blood volume changes, hepatic blood flow, and urinary electrolyte studies are reported which bear on the concept of the post-sinusoidal outflow block and on the metabolic pattern of secondary hyperaldosteronism which accompanies cirrhotic ascites.

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THE USE OF AUTOGENOUS SKIN AS A VASCULAR PROSTHESIS

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ONE OF THE MAJOR PROBLEMS remaining in the field of vascular surgery is the selection of material for use as a replacement graft. As is true in all new arts and sciences, fresh ideas come along faster than old ones can be evaluated. The homograft was thought for several years to be the only possible substitute for the resected segment of an artery, but in the past few years the synthetic fabrics have come to replace the homograft in most surgical centers, and even now few surgeons consider the problem completely settled. The major disadvantages of the homograft are only partially corrected by the synthetic fabrics, which are essentially foreign materials and have all of the theoretic disadvantages which one might expect from the suture of living tissue to a foreign body.

The problems associated with the use of both the homograft and the synthetic prosthesis have prompted re-evaluation of a very old idea—the use of some type of autogenous material, for example, vein. An attempt has been made in this present study to evaluate one particular autogenous tissue, namely skin, for its possible use as a vascular prosthesis.

HISTORICAL REVIEW

The advantages of the nonantigenic, nonforeign nature of an individual's own tissues have been studied by surgeons since the time of Alexis Carrel, and the search for a suitable vascular autograft has led to investigation of various tissues including fascia, vein, pericardium, and skin. Rehn, who in 1914 re-enforced a hernia repair with dermis, was probably the first to use the skin as a deeply implanted autograft in a significant clinical series. In 1939, Peer reported a histologic study of deeply implanted full-thickness skin in experimental animals; he found that within a few months the dermis had undergone complete metamorphosis to dense connective tissue with atrophy of almost all of the sebaceous glands and hair follicles. Uihlein, in 1939, further showed that if the epidermis is removed and only the dermis implanted, no epithelium-lined cysts such as those which have been found by other investigators will form.

Hardin, Horton, Fisher, Pratt and their co-workers have reported the use in dogs of arterial grafts constructed from the dermal layer of skin. In these experiments, the epidermis was removed with a dermatome. The dermis was then dissected free and the fat removed from its deep surface. A tube was fashioned from an area of dermis thus prepared and was placed so as to bridge an experimentally created defect in the aorta. Most of the dogs in each of these experiments died within a few weeks either of thrombosis or rupture of the graft, and the results were generally considered discouraging.

In January, 1957, Wagner and associates (10) made a preliminary report on 6 dogs in which they had used a dermal autograft to bridge a defect in the abdominal aorta. Five of the 6 dogs lived beyond the early postoperative period; 1 lived as long as 6 months with a patent graft (11). Despite the results which have been described in previous reports, the idea of employing the dermis as a vascular autograft seemed reasonable to us.

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Abridgment of thesis submitted by Dr. Crilly to the Faculty of the Graduate School of the University of Minnesota in partial fulfillment of the requirements for the degree of Master of Science in Surgery.

METHOD

For our experiments, we constructed an arterial autograft of the dermal layer of skin and designed it to permit end-to-end anastomosis in the abdominal aorta of dogs. Thirty mongrel dogs weighing 15 to 20 kilograms were used and all operations were done under intravenous pentobarbital sodium (nembutal) anesthesia. With a Padgett dermatome set at about 15/1,000 inch, a split thickness of skin measuring 4 by 6 centimeters was obtained from the upper abdominal wall. This tissue, consisting essentially of epidermis, was discarded, and the underlying area of dermis was dissected away from the body wall. The fat and subcutaneous tissue were dissected from the deep surface of this layer, essentially of dermis or corium.

Through a long midline incision, the abdominal aorta was exposed and its diameter evaluated. A rectangle was then carefully cut from the piece of prepared corium. This area of dermis was exactly 4 centimeters long and, depending on rough evaluation of the diameter of the host aorta, 2.5 to 3 centimeters wide. More exact measurement of host and graft diameters were found, for reasons discussed later, to be useless. The rectangle of dermis was then fashioned into a tube 4 centimeters long, with the smooth, raw, superficial, subepidermal surface turned in to face the lumen of the graft. The tube was sutured lengthwise with a continuous everting No. 5-0 arterial silk suture and was bathed in saline solution until the host aorta was fully prepared. This preparation consisted of ligating 1 or 2 lumbar arteries about halfway between renal and iliac arteries, applying Potts clamps, and excising a small segment of the aorta. The length of the excised segment was such that, when added to the distance of retraction of the ends of the vessel, a defect of 4 centimeters resulted, thus allowing the dermal graft to be inserted end to end under a minimum of tension. The graft was then placed in position and sutured to the host vessel with a continuous No. 5-0 silk suture in accordance with standard vascular surgical techniques.

FIG. 1. Aortogram (dog 8) made 4 months after operation shows occlusion of graft and rich collateral circulation. Dog was clinically well.

The dogs were observed several times a day in the early postoperative period, and subsequently underwent aortographic examination at 4 to 6 month intervals. The aortographic method used was the easy, uniformly successful one described by Boerema and Blickman.

FINDINGS

No operative deaths occurred, and each graft was observed to be patent at the close of the procedure. Ten of the 30 dogs died within the first 16 days and it was noted that one of the suture lines of the graft had ruptured. Three dogs died within 20 days following occlusion of the graft by acute thrombosis. Six dogs were clinically well but were found to have an occluded graft at the time of the first routine aortogram. Figure 1, an aortogram made 4 months after operation, shows that in spite of an occluded abdominal aorta a dog may live indefinitely. The rich collateral circulation completely bypassed the site of the graft and allowed this animal to live in what appeared to be good health. The animal was sacrificed after this aortogram had been made, and the graft was found to be completely filled with a well organized thrombus.

One dog died following separation of the wound and evisceration at 7 days; the graft had remained patent and undilated. In 1 dog there was roentgenographic evidence of a patent graft at 4 months, but the dog died

a

b

c

FIG. 2. Aortograms of dog 16: a, 4 months after operation; b, 8 months after operation; c, 13 months after operation. The irregularities of the graft are essentially the same in a, b, and c, and the variations in diameter evident on the aortograms are probably the same as those noted at operation.

following rupture of a suture line of the graft at 8 months.

Nine dogs lived for periods ranging from 1 to 2 years with grafts that were demonstrated to be patent by serial aortography. One of the 9 dogs living more than 1 year died at 13 months from rupture of a dilated part of the graft. It is not clear whether this dilatation represented a true aneurysm or simply an error in the original construction of the graft, but this was the only dog in the series in which the possibility of true aneurysm formation was seriously considered. The other dogs in this group were sacrificed 1 to 2 years after the operation, necropsy confirming in each case the roentgenologic finding of patency of the graft.

The aortograms demonstrated the definite possibility of successful long term function of this type of vascular prosthesis. In general, each graft appeared on the first aortogram about as might have been predicted from its appearance at the close of operation, and it maintained approximately the same configuration on subsequent aortograms. Figure 2 shows the aortograms of dog 16 made 4, 8, and 13 months after operation. It can be seen that there was very little change in the graft throughout the period of observation. The dermis appears to have maintained its strength, and there is no progressive compromise of the lumen.

The differences of elasticity in different areas of the corium make it very difficult to cut out a rectangle of tissue which, when formed into a tube and subjected to the dog's intraluminal blood pressure, will turn out to have a predictable diameter. For this reason, some of the grafts appeared to have developed a small aneurysm immediately upon release of the Potts clamps. However, these have maintained the same appearance at all subsequent aortographic examinations and finally at necropsy, and we believe this to be a good indication that if the area of dermis is of the optimal thickness in the first place, true aneurysmal dilatation of the graft will not occur. Figure 3 shows the aortograms of dog 7 made 3, 7, 12, and 22 months after placement of the graft. Despite slight irregularities of the graft, probably caused, as already explained, by variations in elasticity of different areas of the dermis, it functioned as well as could be expected of any prosthesis until the animal was sacrificed.

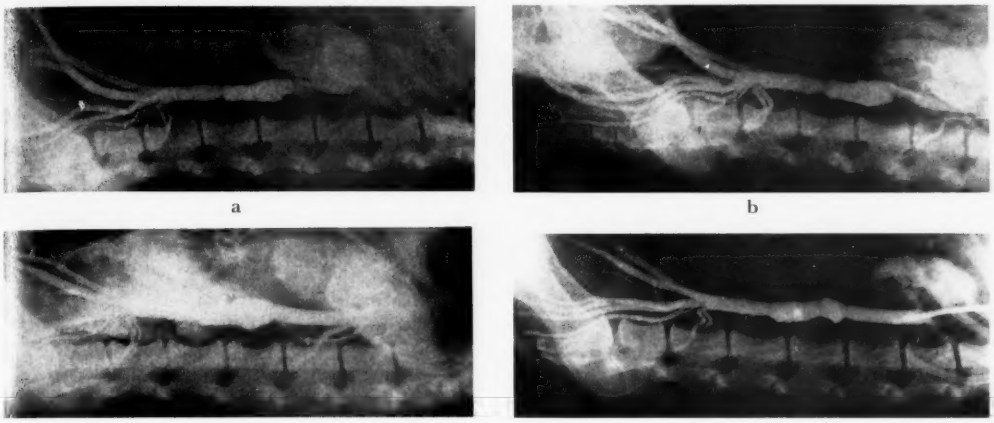


FIG. 3. Aortograms of dog 7: a, 3 months after operation; b, 7 months after operation; c, 12 months after operation; d, 22 months after operation. There was no significant change in the configuration of the graft throughout the period of observation.

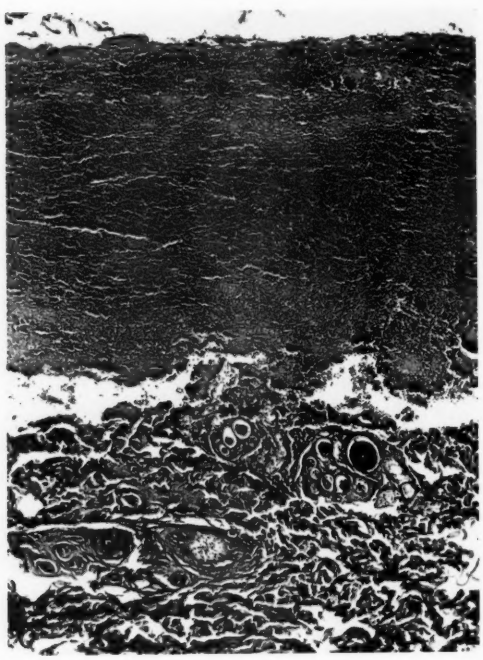
Equally as important as the roentgenologic follow-up is the microscopic follow-up of the progressive changes in a graft of this type. The work of Rehn, Uihlein, and others indicates that deeply implanted dermis undergoes complete metamorphosis within a few weeks to dense connective tissue with atrophy of all skin appendages. But does the same thing happen to dermis used as an arterial prosthesis?

Figure 4a represents a section through the luminal surface of a dermal graft that was patent when the dog died, after separation of the wound and evisceration, on the seventh postoperative day. When the graft was opened and the fresh thrombus washed away, the surface appeared essentially as it had at operation 7 days before. The rough irregular arrangement of the fibrous tissue of the dermis can be seen. The hair shafts near the surface are seen to be associated with follicles and sebaceous glands in early stages of atrophy.

Figure 4b represents a section through the surface facing the lumen of a dermal graft that was patent when the dog was sacrificed 22 months after operation. The dense nature of the connective tissue, the smooth surface facing the lumen, and the small blood vessel in close relationship with the external surface of the graft are evident. Of special interest are the hair shafts with which are associated no follicles or glands and no evidence of cyst formation. Instead, however, the hair shafts are isolated by dense connective tissue.

Figure 5 represents a cross section of another graft that was in place for 13 months. The same orderly arrangement of the fibrous tissue seen in Figure 4b may also be noted here. At necropsy, no evidence of hair growth was seen grossly in any of the grafts or microscopically in any of the tissue sections. We believe that hair and associated follicles and glands are not a problem in the use of this type of autograft.

Of obviously great importance is the histology of the line of anastomosis—the union of the normal artery and the dermal graft. At first, of course, there is simply a mechanical union held fast by the silk suture. Figure 6 shows the anastomosis of a graft that was in place for 3 days. The loose rough connective tissue of the dermis abuts securely against the dense elastic tissue of the normal artery. There is no continuity of any of the tissue elements across the suture line from artery to graft. The early unorganized



a

b

FIG. 4.

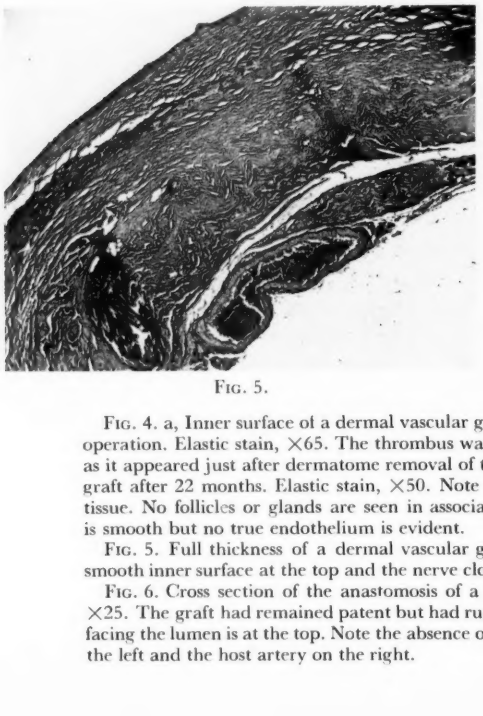


FIG. 5.

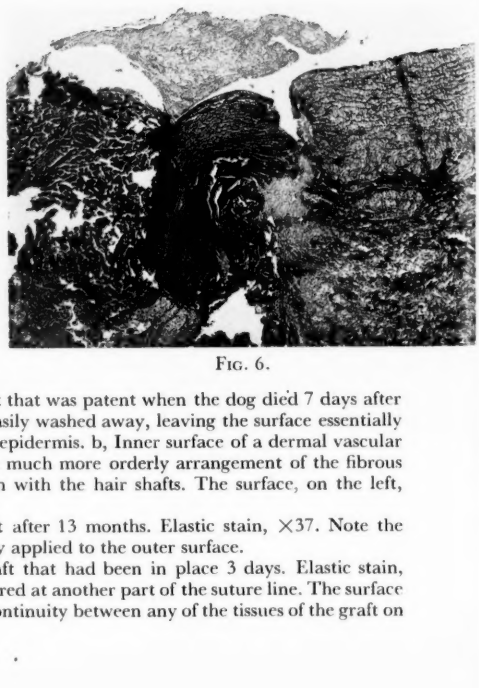


FIG. 6.

FIG. 4. a, Inner surface of a dermal vascular graft that was patent when the dog died 7 days after operation. Elastic stain, ×65. The thrombus was easily washed away, leaving the surface essentially as it appeared just after dermatome removal of the epidermis. b, Inner surface of a dermal vascular graft after 22 months. Elastic stain, ×50. Note the much more orderly arrangement of the fibrous tissue. No follicles or glands are seen in association with the hair shafts. The surface, on the left, is smooth but no true endothelium is evident.

FIG. 5. Full thickness of a dermal vascular graft after 13 months. Elastic stain, ×37. Note the smooth inner surface at the top and the nerve closely applied to the outer surface.

FIG. 6. Cross section of the anastomosis of a graft that had been in place 3 days. Elastic stain, ×25. The graft had remained patent but had ruptured at another part of the suture line. The surface facing the lumen is at the top. Note the absence of continuity between any of the tissues of the graft on the left and the host artery on the right.

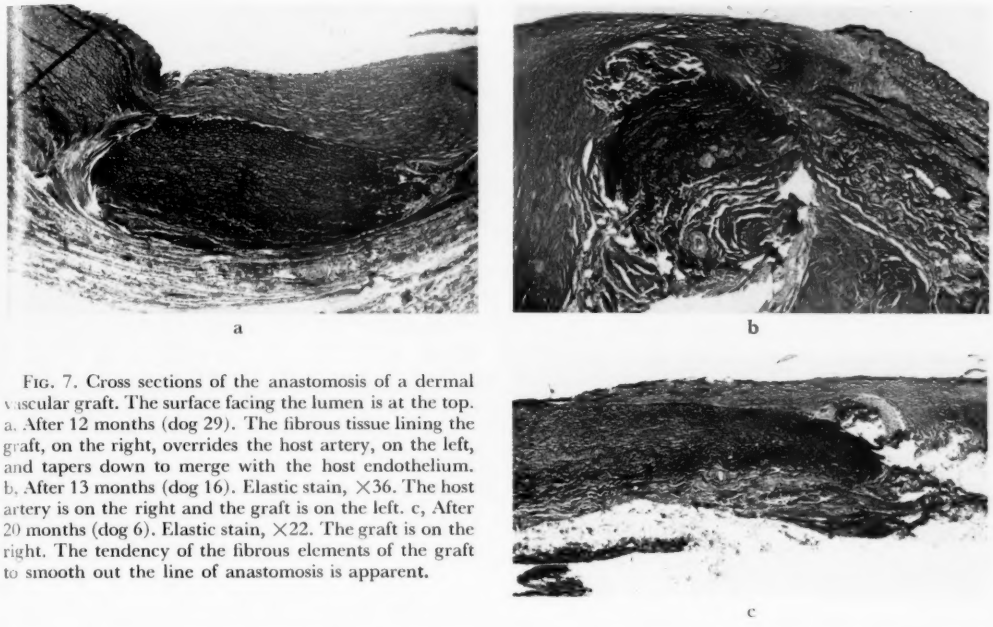


FIG. 7. Cross sections of the anastomosis of a dermal vascular graft. The surface facing the lumen is at the top. a, After 12 months (dog 29). The fibrous tissue lining the graft, on the right, overrides the host artery, on the left, and tapers down to merge with the host endothelium. b, After 13 months (dog 16). Elastic stain, ×36. The host artery is on the right and the graft is on the left. c, After 20 months (dog 6). Elastic stain, ×22. The graft is on the right. The tendency of the fibrous elements of the graft to smooth out the line of anastomosis is apparent.

thrombus seems to be attached just at the junction of the two tissues. As in the case of plastic graft materials, a thin fibrinoid layer probably covers the inner surface of the microscopically rough graft very early, smoothing out the irregularities of its intimal surface and filling the crevice at the line of anastomosis. Figure 7 represents 3 different dermal grafts that were in place and patent for 12, 13, and 20 months respectively. These cross sections are taken at the line of anastomosis. Suture material pervaded with much fibrous tissue can be seen in each section, and the absence of tissue reaction around this foreign material is to be noted. The nature of the union of the two tissues is striking. The smooth fibrous tissue lining the dermal graft has come to override the dark-staining elastica of the host artery, smoothing out the line of anastomosis and tapering down to merge with the intima of the host. It is at once apparent that blood should flow over such an anastomosis without any difficulty.

The question of endothelial covering of the dermal graft is not answered by this histologic study. It is not answered, as a matter of fact, in the case of any type of prosthesis. A few cells, which may be endothelium, can be seen overlying the dermis in some of the sections, but the most likely possibility is that, just as is generally thought to be true of plastic grafts, the smooth fibrous lining of the graft serves adequately as an intima without ever developing a cellular surface.

Many questions, of course, remain unanswered by this study. But the possibility of the use of dermis in vascular surgery is demonstrated, and perhaps encouragement to further investigation may be found here. Clinical use of this type of autograft would probably be justified only after many more experimental trials.

SUMMARY

The dermal layer of skin was used as a vascular autograft in the abdominal aorta of 30 dogs. The results, including the histologic findings, indicate that this type of autograft may have a place in the field of vascular surgery.

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LYMPH NODE REACTIVITY IN CANCER PATIENTS

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IN PREVIOUS ARTICLES we reported on some of the structural and cytologic features of lymph nodes removed at autopsy from noncancer patients and studied with the use of routine hematoxylin and eosin and ammoniacal silver staining (1,2). There appeared to be a correlation between the lymph node pattern and the type of disease which caused or was associated with the death of the patient. In particular, such studies (3) confirmed and extended previous reports on the response of lymphoreticuloendothelial system to antigenic stimulation.

We also observed that the presence of spontaneous mammary cancer in mice was associated with a variety of reactive changes in their lymph nodes (5). In addition, extensive studies of human lymph nodes stained with hematoxylin and eosin provided data on the prognostic significance of lymph node structure in cancer patients. In the present study we applied the silver technique to axillary lymph nodes obtained at autopsy from diverse types of cancer patients. A parallel study has also been made on the lymph nodes obtained in the course of radical mastectomy for carcinoma of the breast. The findings were compared with those obtained from studies of peripheral lymph nodes in an extended series of noncancer patients. In general, the peripheral lymph nodes in individuals with systemic disease exhibit similar lymph node patterns.

MATERIAL AND METHODS

The present report is based on a study of superficial lymph nodes from 270 patients of the following types: Autopsy cancer cases.—Axillary lymph nodes were obtained from a series of 47 cancer cases, viz., prostate, 3; lung, 10; esophagus, 2; stomach, 1; pancreas, 2; rectum, 2; breast, 6; colon, 2; cervix, 2; myeloma, 1; palate, 1; brain, 1; ovary, 3; lymphosarcoma, 3; Wilm's tumor, 1; gallbladder, 1; liver, 2; neuroblastoma, 1; urinary bladder, 1; and carcinomatosis, primary site undetermined, 2 cases. Surgical breast cancer.—Axillary lymph nodes were obtained in the course of radical mastectomy in 29 unselected cases of breast carcinoma. In addition, a study was made of the axillary lymph nodes from a series of 26 patients with breast carcinoma surviving 5 years postoperatively and a series of 19 breast cancer patients who died of their disease less than 3 years postoperatively. The data obtained in the cancer series were compared with those from a surgical and autopsy series of noncancer cases. The noncancer cases represented an extension of a previously reported series (1). Peripheral lymph nodes—axillary, cervical, inguinal—were obtained surgically from 38 patients, the biopsies being performed for diagnostic purposes because of local lymphadenopathy. In 5 of these cases, tuberculosis was present. The remaining 33 cases were instances of lymph node enlargement secondary to obvious or occult local infection or irritation.

Axillary lymph nodes were also obtained at autopsy from 117 noncancer patients. This series included the following types of cases: acute deaths—postoperative deaths, cerebrovascular accidents, cardiac decompensation, and myocardial infarctions—48 cases; acute infectious diseases, 41 cases; pulmonary tuberculosis, 8 cases; and cirrhosis or uremia 20 cases.

In all instances the lymph nodes were fixed in 10 per cent neutral formalin. Routine 5 micron paraffin sections were prepared in duplicate, one section being stained with hematoxylin and eosin while the other

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was stained with ammoniacal silver according to our previously described method (3).

The hematoxylin and eosin stained sections were systematically examined with regard to the following features: type of pulp—lymphoid or reticuloendothelial; prominence of plasma cell aggregates in the medullary cords; prominence of secondary follicles; prominence of eosinophilic leucocytes; prominence of sinusoids; character of the sinusoidal contents, viz., acellular fluid, macrophages, syncitial histiocytes—vacuolated or nonvacuolated; and sinus histiocytosis. Note was also taken of granulomatous foci, hyalinization, and amyloid changes as well as metastases to the nodes.

The silver-stained sections were evaluated in terms of nuclear staining of the lymphoid cells and the prominence and type of metallophils—silver stained reticular cells—in the pulp, sinusoids, and littoral cells of the sinusoids. The characteristics of lymph nodes were recorded and each case was then designated as to lymph node pattern.

Since lymph nodes undergo sequential changes in response to different stimuli, the designation of pattern is arbitrary. However, such designation serves as a tool for investigating the relationship between lymph node structure and biologic events. Some of the groupings used in this study may prove to be divisible as more data become available. On the other hand, certain other patterns might eventually be grouped together. With these limitations in mind, the characteristics of the various patterns employed in the present study were as follows.

Control. Such nodes are normoplastic. The pulp is lymphoid in type. Follicles, plasma cells, and eosinophils are uncommon. The sinusoids are usually narrow or only moderately prominent and contain scattered rounded macrophages or occasional lymphocytes or both. Silver staining visualizes stellate reticular cells in the pulp and the metallophilic cytoplasm of the sinus macrophages. Occasional fusiform metallophils may be seen in sinusoids. However the lining cells of the sinusoids—littoral cells—are not well stained. The lymphoid cells are unstained.

Phagocytosis. Such nodes are similar in appearance to the control pattern but are characterized by an increased prominence of sinusoidal macrophages and pulp metallophils. In the present report this group has not been subdivided according to the types of phagocytosis, viz., particle phagocytosis, vacuolated phagocytosis, nonvacuolated phagocytosis, and erythrophagocytosis.

Recognition. The structural features are similar to those of the control or phagocytosis patterns. However, the nuclei of the lymphoid cells are stained with silver while the metallophil cells are essentially similar to those in control or phagocytosis patterns.

Immune-reactive. The structure of these nodes is similar to that of the reactive pattern. However, the follicles tend to be less prominent while the sinusoids contain an increased number of fusiform and stellate histiocytes. These histiocytes which may have vacuolated or nonvacuolated cytoplasm are stained intensely with silver. The pulp metallophils are enlarged and exhibit increased branching of their cytoplasmic processes. In addition, the littoral cells of the sinusoids exhibit distinct metallophilia. Metallophil cells may also be seen in the secondary centers. Nuclear staining of the lymphoid cells is usually present to some degree, or else some of the nodes may have a reactive type pattern while others have an immune pattern.

Immune, follicular. The structure is similar to the reactive pattern with particularly prominent follicles. However, the nuclei of the lymphoid cells are not stained with silver. Hypertrophied silver-stained reticular cells are seen in the follicles, but the pulp and sinusoidal metallophils are not unduly prominent.

Immune, sinus. The structure is similar to that of the reactive-immune pattern with some decreased prominence of follicles. After silver staining, pulp, sinusoidal, and littoral cell metallophilia is marked. Follicular metallophils may or may not be present.

Nuclear staining of the lymphoid cells is minimal or absent.

Exhausted. The structure resembles the reactive pattern but tends to be somewhat hypocellular and edematous. After silver staining, there is no appreciable staining of either the reticular or lymphoid cells.

Syncytial histiocytosis. The nodes are hyperplastic. The pulp is usually lymphoid in type, while the follicles are of minimal or moderate prominence. Plasma cells and eosinophils are usually present in the medullary cords. The sinusoids are moderately or markedly dilated and contain elongated histiocytes which have a fibrillary or finely vacuolated appearance.

Silver staining reveals a syncytium of fusiform metallophils in the sinusoids, minimal to moderate staining of the littoral cells, and prominent branching metallophils in the pulp. A faint to moderate nuclear staining is commonly observed in the cortical lymphoid cells.

Sinus histiocytosis. This pattern is characterized by a hyperplastic lymphoid pulp, minimal secondary follicles, and minimal plasma cells and eosinophils in the medullary cords. The sinusoids are moderately or markedly dilated and contain elongated syncytial histiocytes having a nonvacuolated eosinophilic cytoplasm. After silver staining, the sinus histiocytes exhibit a distinct perinuclear condensation of silver staining so that the extended cytoplasmic processes and syncytial relationship are not readily apparent. The littoral cells and pulp metallophils are of minimal or moderate prominence.

Degenerative syncytial histiocytosis. The appearance after hematoxylin and eosin staining is that of atrophic changes in syncytial histiocytosis with sinusoidal edema and coarse vacuolization of the syncytial histiocytes. With the silver technique fragmentation is seen with loss of clarity of staining of the syncytial histiocytes. The pulp metallophils are rounded and their cytoplasmic processes are withdrawn and coarse.

Degenerative reticuloendotheliosis. The appearance after hematoxylin and eosin staining is similar to the phagocytosis or reactive patterns; however, the node looks edematous, and numerous large macrophages are seen in the sinusoids. The silver technique reveals clumping and degenerative changes in the pulp metallophils. The sinus macrophages have irregular vacuolated cytoplasmic staining of moderate or poor intensity. The lymphoid cell nuclei are unstained.

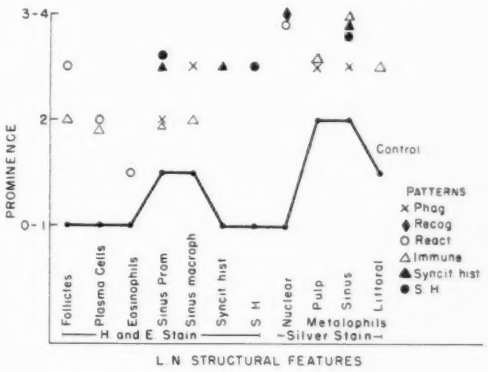

FIG. 1. Prominence of various structural features of control lymph node as seen with hematoxylin and eosin and silver staining. The deviations from the control pattern are indicated for the various responsive patterns.

Degenerative sinus histiocytosis. Hematoxylin and eosin staining reveals vacuolization of the sinus histiocytes, hyalinization and/or fibrotic changes. After silver staining the sinusoidal metallophils show a granular fragmentation of the silver staining. There is no appreciable staining of the reticular cells of the pulp, littoral cells, or lymphoid cells. In the present report the cases of degenerative sinus histiocytosis and degenerative syncytial histiocytosis have been combined under the latter heading. In Figure 1 a schematic illustration is presented of the characteristics of the control pattern and the variations from this pattern as found in the different responsive patterns.

RESULTS

Autopsy series, cancer patients. In 9 of the 47 cancer cases, the axillary lymph nodes con-

tained metastases: viz., stomach, 1; breast (contralateral), 3; lung, 2; ovary, 1; prostate, 1; and carcinomatosis, 1. In 4 of these cases, the metastatic involvement was so extensive that it was impossible to evaluate the lymph node structure. In a number of these nodes, the involvement was greater in the medullary region than in the peripheral sinuses. These data as well as the lack of direct lymph vessel drainage from parenchymal tumor foci suggest that lymph node metastases may be hematogenous as well as lymphogenous in origin.

The structural features of the axillary nodes, as seen in hematoxylin and eosin stained sections from the 43 patients with readable nodes, were as follows: The pulp was lymphoid in type in 42 of 43 cases and tended to be hypocellular with areas of hyalinization. In only 1 of the cases was there any appreciable reticuloendotheliosis of the pulp. Follicles were minimal or absent in 41 of the cases and moderately prominent in 2 cases. Plasma cells were sparse in 33 cases, moderately prominent in 7 cases, and numerous in only 3 of the 43 cases. Aggregates of eosinophilic leucocytes were seen in the medullary cords in only 3 cases. The sinusoids were narrow or inconspicuous in 8 cases. In the remaining 35 cases the sinusoids were distinct or prominent. In 9 of the cases the sinusoids contained rounded macrophages which were usually vacuolated. In 20 cases the sinusoids contained syncytial histiocytes which showed varying degrees of hyalinization, vacuolization, and fibrosis. In only 1 instance were such degenerative changes absent from the syncytial histiocytes. No instance of sinus histiocytosis was encountered in this series of autopsy cases.

Thus, in composite, the hematoxylin and eosin stained lymph nodes from the autopsy series were characterized by a moderately hypoplastic lymphoid pulp, minimal secondary follicles, plasma cells, and eosinophils. The sinusoids tended to be prominent and contained degenerative appearing histiocytes. Areas of hyalinization, amyloid changes, and fibrosis were common in the pulp and sinusoids.

The lymph node patterns, as judged by the combined use of hematoxylin and eosin and silver staining are indicated in Table I. In 15 of the 43 cases there was silver staining of the lymphoid cell nuclei. Superimposed preterminal infections were present in the majority of the cases with nuclear staining, viz., peritonitis, pyelonephritis, and pneumonia. Only 1 of these cases was classified as having an immune pattern.

The majority (74 per cent) of the total cancer series was considered to have some type of degenerative pattern, viz., degenerative reticuloendotheliosis, degenerative syncytial histiocytosis, or exhausted. In essence, it appeared that the lymph nodes of those dying of cancer were characterized by degenerative changes of reticuloendothelial cells.

Comment should also be made on the frequency of erythrophagocytosis in the axillary nodes from the autopsy series of cancer cases. In approximately 28 per cent of the cases there was prominent erythrophagocytosis with hemosiderin crystals in the sinusoidal areas of the nodes. These findings may be pertinent to the development of acquired hemolytic anemia in far advanced cancer. Clinical studies by Ultmann have emphasized the role of the spleen in this phenomenon. It may be that the lymphoreticuloendothelial system of the lymph nodes also participates in the increased rate of red cell destruction.

Breast cancer, unselected, current series. In general the axillary nodes removed in the course of radical mastectomy had a hyperplastic appearance. In 15 of the cases, there was distinct reticuloendotheliosis of the pulp, and in 1 instance the nodes showed extensive sarcoid-like transformations. The follicles were inconspicuous in 19 cases, moderately prominent in 8 cases, and markedly prominent in 2 cases. Plasma cells were minimal in 20 cases, but moderately frequent in 9 cases. However, eosinophils were essentially absent in all the cases. The sinusoids were moderately or markedly prominent in 24 cases

TABLE I.—PER CENT INCIDENCE OF LYMPH NODE PATTERNS IN RELATION TO DISEASE

Group	*No. cases*	*Control*	*Phagocytosis*	*Recognition*	*Reactive*	*Reactive-immune*	*Immune, follicle*	*Immune, sinus*	*Syncytial histiocytosis*	*Sinus histiocytosis*	*Degenerative reticuloendotheliosis*	*Degenerative syncytial histiocytosis*	*Exhausted*	*Sarcoid-like*
Autopsy														
Acute death	48	44	38	13	6									
Acute infection	41		22	37	17	5							19	
Tuberculosis	8											100		
Cirrhosis-uremia	20		10	10					50			15	15	
Cancer	41		7	19				2			17	42	15	
Surgical														
Noncancer or tuberculosis	33		15	9	15	6	3	33	12				6	
Tuberculosis	5							40	60					
Breast cancer														
Current series	29		17	7	3	3		17	17	3		24	3	3
5 yr. survival	26	4	12	8		4	4	19	23	19		4	4	
Died within 3 years	19		16	5							5	63	10	

in this series. They contained macrophages in 5 cases, nonvacuolated syncytial histiocytes in 8 cases, vacuolated histiocytes in 8 cases, and sinus histiocytes in 3 cases.

In essence, the hematoxylin and eosin stained lymph nodes were characterized by reactive changes with a tendency toward sinus reticuloendothelial cell proliferation. The lymph node patterns as defined by the combined use of hematoxylin and eosin and silver staining are indicated in Table I. In 3 of the cases there was distinct silver staining of the nuclei of the lymphoid cells. Two of the cases was considered to have a recognition pattern, while 1 had a reactive pattern. In 12 of the 29 cases, the patterns gave evidence of an advanced degree of lymph node response, viz., reactive-immune, 1; immune, sinus, 5; syncytial histiocytosis, 5; and sinus histiocytosis, 1 case. In only 7 of the cases were degenerative patterns encountered. Thus, in contrast to the findings in the autopsy series, the lymph nodes of the surgical series were characterized by proliferative activity, particularly in their reticuloendothelial cells.

Breast cancer, 5 year survival series. The axillary lymph nodes in this series tended to be hyperplastic. In 9 of the 26 cases, there was a distinct reticuloendotheliosis of the pulp. Follicles were markedly prominent in only 1 case and moderately prominent in 11 cases. Plasma cells were minimal in 18 cases and moderately distinct in 8 cases. Eosinophils were rare in all cases. The sinusoids were moderately or markedly prominent in 23 cases and contained sinus histiocytosis cells or nonvacuolated syncytial histiocytes in 11.

In general the hematoxylin and eosin stained lymph nodes in this series were characterized by hyperplastic features which were particularly manifest in the sinusoidal reticuloendothelial cells. The lymph node patterns as defined by the hematoxylin and eosin and silver staining are indicated in Table I. Advanced responsive patterns were found in 18 cases: viz., reactive-immune, 1; immune, follicle, 1; immune, sinus, 5; syncytial histiocytosis, 6; and sinus histiocytosis, 5. Degenerative patterns were found in only 2 of the 26 cases. The frequency of responsive patterns, particularly those of the sinus reticuloendothelial cells, was the dominant feature of this series (Figs. 2 and 3).

Breast cancer, dead in less than 3 years postoperatively. In this series 7 of the 19 patients had reticuloendotheliosis of the nodes. The follicles were markedly prominent in 1 case and moderately prominent in 2 cases. Plasma cells were marked in 1 case and moderate in 7 cases. The sinusoids were marked in 1 case and moderate in 14 cases. However, the reticuloendothelial cells in the sinusoids tended to be vacuolated and degenerative appearing.

Table I contains a listing of the lymph

FIG. 2. Axillary lymph node, breast cancer patient surviving 5 years postoperatively. Hematoxylin and eosin.

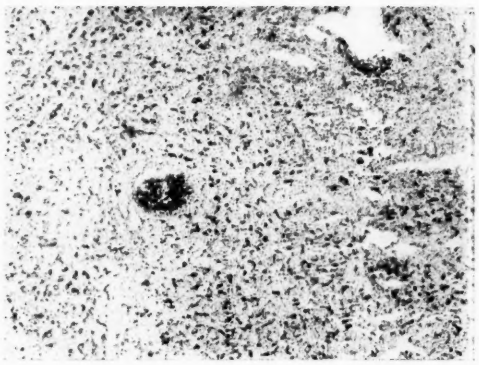

FIG. 3. Axillary lymph node, breast cancer patient surviving 5 years postoperatively. Ammoniacal silver staining.

node patterns in this series. Responsive patterns were absent while degenerative patterns were found in 15 of the 19 cases. These data are similar to those in the cancer autopsy series and in contrast with the finding in the 5 year survival cases.

Autopsy series, noncancer patients. In Table I, the frequency of the various lymph node patterns encountered in the noncancer cases is listed. These cases have been subdivided into 4 groups: acute death (noninfectious), acute infectious, tuberculosis, and the uremia-cirrhosis.

In 82 per cent of the acute death series, the nodes had control or phagocytosis patterns. In 6 of the 48 cases, the nodes had a recognition pattern, and in 3 cases the pattern was reactive.

In the acute infection series, silver staining of the lymphoid cell nuclei occurred in 54 per cent of the cases; viz., recognition pattern, 37 per cent; reactive pattern, 17 per cent. In further contrast to the acute death series, an exhausted pattern was observed in 8 of the 41 cases (19 per cent).

All of the 8 patients who died of active pulmonary tuberculosis exhibited the degenerative syncytial histiocytosis pattern in the lymph nodes.

In the uremia-cirrhosis group, the lymph nodes in the majority of the cases had the syncytial histiocytosis pattern. Degenerative patterns in the form of degenerative syncytial histiocytosis and exhausted were found in 30 per cent of the cases.

The 38 cases of peripheral node biopsies may be considered in two groups: tuberculosis, 5 cases, and nontuberculosis, 33 cases.

The disease in the tuberculosis cases was fairly well controlled. None of the patients were debilitated and all were ambulatory. The nodes in this series had syncytial histiocytosis patterns in 3 cases and an immune pattern in 2 cases. This is in contrast with the degenerative patterns found in the autopsy series.

In the nontuberculosis cases, node enlargement was a local phenomenon in response to a regional irritation or infection. As indicated in Table I, the nodes exhibited a variety of reactive changes. They were characterized by secondary follicles, plasma cells, eosinophils, and nuclear staining of the lymphoid cells. In more than 40 per cent of the cases, the node patterns were reactive-immune or immune. On the other hand, syncytial histiocytosis or sinus histiocytosis patterns were uncommon (12 per cent).

COMMENTS

One of the most striking findings of this and our previous studies is the confirmation of lymph node responsiveness to biologic events. Knowledge of lymph node structural

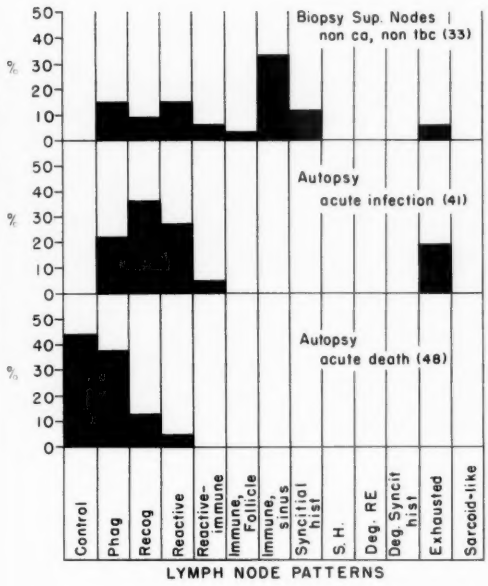

Fig. 4.

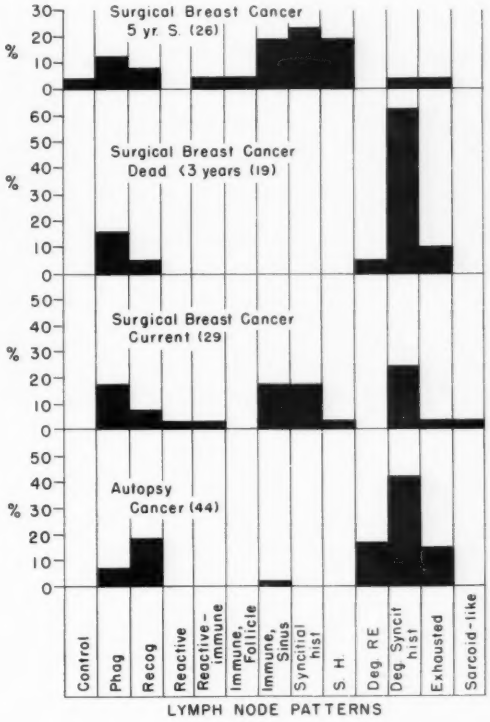

Fig. 5.

Fig. 4. Lymph node patterns of noncancer cases.
Fig. 5. Lymph node patterns of cancer series.

and functional characteristics during various disease processes might provide more insight into the nature of obscure diseases.

The comparative features of the lymph node patterns in the various groups are depicted in Figures 4 and 5. The acute infectious disease groups were characterized by those patterns involving silver staining of the lymphoid cell nuclei (recognition and reactive), follicle and plasma cell formation, and stimulation of the reticuloendothelial cells of the pulp and the littoral cells—reactive-immune, immune, follicle, immune, sinus, and exhausted. In those patients dying from or with acute infectious diseases, the progressive response was largely limited to the early phases—recognition and reactive and the exhausted pattern. In contrast, in nodes draining apparently controlled local lesions the immune patterns were most frequent.

On the other hand, the cancer series was characterized by stimulation and/or degeneration in the sinus reticuloendothelial cells. In the autopsy series of cancer cases, despite some instances of terminal infection, the dominant feature was degenerative changes in the sinusoidal reticuloendothelial cells—degenerative reticuloendotheliosis, degenerative syncytial histiocytosis, and degenerative sinus histiocytosis. A similar profile of lymph node patterns was observed in the breast cancer series of patients who died less than 3 years postoperatively. In both of these series, the immune, sinus, syncytial histiocytosis, and sinus histiocytosis patterns were rare. In contrast, these latter patterns dominated the profile in the series of breast cancer patients who lived more than 5 years postoperatively whereas the degenerative patterns were uncommon. As might be expected, the unselected series

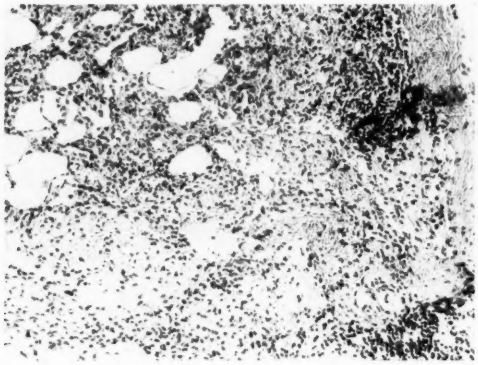

FIG. 6. Axillary lymph node at autopsy from breast cancer patient treated with nitrogen mustard. Hematoxylin and eosin staining.

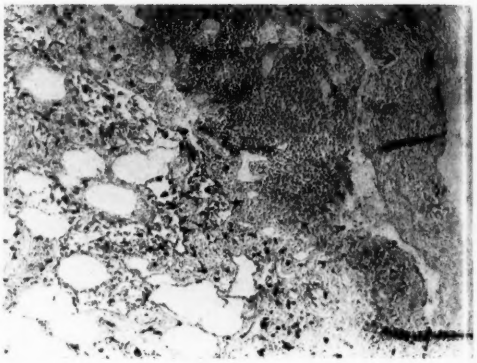

FIG. 7. Axillary lymph node at autopsy from breast cancer patient treated with nitrogen mustard. Ammoniacal silver staining.

of breast cancer cases included both responsive and degenerative patterns.

Before considering the findings in the cancer cases, it would be desirable to take note of the data obtained in the noncancer series with reference to current concepts in immunology. It is generally held that immunologic reactions are of two main types, usually designated as the hyperimmune and the delayed bacterial hypersensitivity types. The former is characterized by circulating antibodies, usually found in the gamma globulin fraction of the serum proteins. While the ultimate production of such antibodies is a function of plasma cells, there are significant biologic events which precede the development of antibody production by plasma cells in response to antigenic stimulation. These preceding events appear to involve the phagocytic cells of the reticuloendothelial system and the lymphocytes. The hyperimmune type of response seems to be correlated with the sequential lymph node patterns of: phagocytosis, recognition, reactive, reactive-immune, and immune. The exhausted pattern seems to represent the effects of overwhelming amounts of antigen.

On the other hand, delayed bacterial hypersensitivity reactions are characterized by minimal amounts of circulating free antibody. Rather, the antibodies seem to be associated with the lymphoid cells—circulating lymphocytes. This phenomenon is not as distinctly related to plasma cell activity and may occur in agammaglobulinemic individuals. The prototype of such reactions is found in tuberculosis. It is therefore of interest to note that the patterns in the nodes removed surgically from tuberculosis patients differed from those with acute infectious processes. While plasma cells and follicle formation were not particularly prominent in the tuberculosis cases, syncytial proliferations of sinus metallophils and pulp metallophils were outstanding. Furthermore, in the tuberculosis cases, at autopsy, the most striking feature in the lymph nodes was the degenerative changes in the sinusoidal metallophils. It would appear that this system of cells is of importance in maintaining host reactivity against tuberculosis infections.

It is interesting that this system of cells also seems to be involved in the cases of portal cirrhosis and uremia. In these cases, however, plasma cells and eosinophils were more prominent although the most striking feature was the syncytial histiocytosis. It is also noteworthy that in these cases the nodes at autopsy were characterized by responsive rather than degenerative changes as was found in the cases of tuberculosis. The lymph node changes in the cirrhosis-uremia

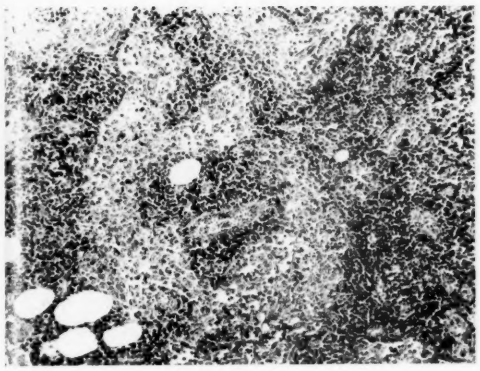

FIG. 8. Axillary lymph nodes, breast cancer case at time of mastectomy. Hematoxylin and eosin staining.

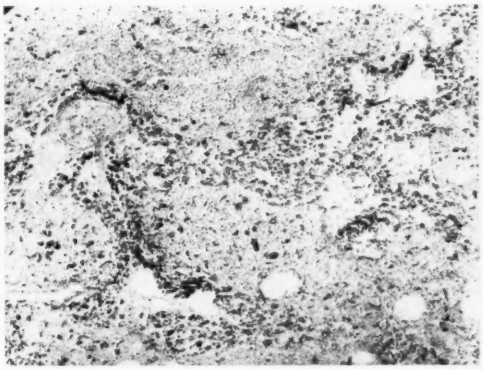

FIG. 9. Axillary lymph nodes, breast cancer case at time of mastectomy. Ammoniacal silver staining.

group may be causally related to the disease, viz., an autoimmune reaction. Plasma cell reactions in cirrhosis have been reported previously by Glagov and associates.

With these various considerations in mind, the data obtained in the cancer cases may be considered. The basic question in regard to immunologic phenomena in human cancer is whether or not the cancer tissue acts as an antigen in its host of origin. Whether cancer tissue does or does not possess antigenicity after transplantation to other humans or experimental animals may be interesting but is not necessarily pertinent to the antigenicity of a spontaneous cancer in the host of origin.

If spontaneous cancers possess antigenicity to their host, then they should produce lymph node changes consistent with a hyperimmune or delayed bacterial hypersensitivity response. However, even if spontaneous cancer tissue possessed antigenicity to its host it does not necessarily follow that this property would perforce evoke a growth-limiting antibody response. It is conceivable that tumor growth potential might override the effect of host antibodies, perhaps via the production of excess antigens with concomitant immunologic paralysis in the sense of Felton. The lymph nodes should reflect such events in the form of degenerative patterns in advanced cases or early responsive nodal reactions which fail to progress to immune responses. In essence, there should be a correlation between lymph node patterns and the biologic behavior.

It is also conceivable that cancer tissues might possess or elaborate antigens which are not critically related to the survival or growth of the tumor. In such an event, the antibody response would have minimal influence on the biologic behavior of cancer, and the lymph node patterns should be without relationship to biologic behavior.

The findings in the majority of the axillary nodes removed during radical mastectomy are consistent with a response to antigenic stimulation. This impression is in keeping with observations on the lymph nodes of mice bearing spontaneous mammary carcinomas. In the mice, however, the node patterns were more consistent with a hyperimmune type of response, while, in the human series, the node reactivity was more varied but tended to be more similar to that seen in tuberculosis. In the autopsy series of cancer patients and in the series of breast cancer patients dying within 3 years after mastectomy the nodes were characterized by distended sinusoids and a tendency toward degenerative changes in the reticuloendothelial cells of the pulp and sinusoids. In this respect, also, they resembled the finding in the patients dying with active tuberculosis.

It would seem from these data that hu-

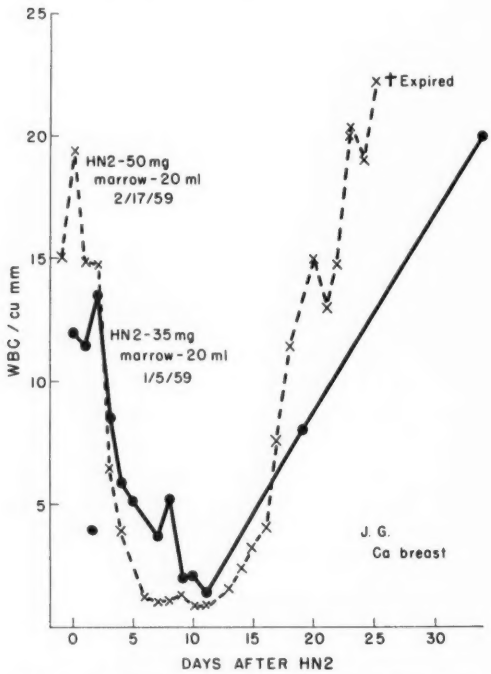

FIG. 10. Effect of nitrogen mustard on white blood cell count in patient given autologous marrow infusion. Note that hematopoietic function was hyperactive before death in contrast to the degenerative status of the lymph nodes.

man cancer tissues might act as an antigen to the host reticuloendothelial system. However, the type of immunologic mechanism involved seems to be more similar to delayed hypersensitivity phenomena than to hyperimmune reactions. Immunologic investigations of the tumor-host relationship might be more profitably directed toward delayed hypersensitivity phenomena rather than toward demonstrating circulating antibodies. It is noteworthy that despite numerous studies, anticancer antibodies have not been conclusively demonstrated in the serum of cancer patients.

The finding that cancer cases tend to have reactive nodes at the time of surgery and degenerative nodes at the time of autopsy may also have implications in regard to certain attempts at cancer chemotherapy. Currently, there is a study being made on the use of various alkylating agents as adjuvants in the primary treatment of cancer. It is well known that the lymphoreticuloendothelial system is particularly sensitive to such agents. With this in mind and in view of our data on lymph node reactivity in the "early" phases of cancer, there is a disturbing possibility that the use of such agents in the early phases of cancer might do more harm than good.

The lymph node damaging effects of alkylating agents may occur without relation to their effect on hematopoiesis. While autologous marrow infusions may protect against the hematologic damage of nitrogen mustard, it does not prevent lymph node damage. Figures 6 and 7 depict the degenerative changes in the axillary lymph nodes of a patient treated with nitrogen mustard for metastatic breast carcinoma. This patient was operated upon for a carcinoma of the right breast in February 1958. The lymph nodes were free of metastases but showed a degenerative syncytial histiocytic pattern (Figs. 8 and 9). By October of 1958, nodular hepatomegaly had developed. On 4 January 1959 she received 35 milligrams of nitrogen mustard as a single intravenous injection after the removal of 20 milliliters of sternal marrow. Ten minutes after the injection the marrow, suspended in saline, was returned intravenously. The effects on her white blood cell count are indicated in Figure 10. The hepatomegaly decreased slightly but then increased again. A repetition of the nitrogen mustard therapy was performed on 16 February 1959 with 50 milligrams of nitrogen mustard. Despite the high dosage there was no regression of the hepatomegaly. On the contrary, the liver enlarged rapidly, and the patient expired on 19 March 1959. Although the peripheral blood count and bone marrow cellularity were hypernormal at the time of autopsy, the lymph nodes exhibited the extreme degenerative changes depicted in Figures 6 and 7. The effects of alkylating agents on host reactivity need further investigation before alkylating agents are used

as a routine adjuvant in the primary treatment of cancer.

The present study also raises a question in regard to cancer therapeutic efforts which are directed toward enhancing host reactivity. Even if such an agent were available it seems unlikely that it would be effective in the advanced stages of the disease in which the lymphoreticuloendothelial system has undergone degenerative changes. Yet such advanced cases are customarily utilized for the testing of all potential therapeutic agents. It would seem reasonable to evaluate alleged host stimulating agents as adjuvants in primary treatment of cancer.

A salient feature which has emerged from our various studies of lymph node reactivity is the relationship between lymph node structure and biologic events (Figs. 4 and 5). Even the simple techniques which have been utilized to date give evidence that much useful information is obtainable from the systematic study of lymph node reactivity. There is a need to extend the scope of the analysis of lymph node reactivity by using additional techniques applicable to the study of lymphoreticuloendothelial activity. Correlation of such data with serologic and biologic events may provide new insight into various disease states.

While the data are consistent with the thesis that the lymph nodes of some cancer patients react to antigenic stimuli, there are several questions that arise, viz.: What is the nature of the antigen(s) and what is its origin? Does the antigen arise from the tumor cells per se or is it derived from alterations in the surrounding stroma or parenchyma? If the antigen is derived from the cancer cell, is it critically related to growth or survival of such cells? Unfortunately, available information does not provide definitive answers to these questions. Our previous studies on sinus histiocytosis of lymph nodes indicated that this lymph node pattern was associated with prolonged survivals (4). This type of reaction pattern would seem to be a response to a critical component in cancer cells. The lymph node patterns in the breast cancer series presented in the present study also suggest a relationship between lymph node structure and survival. Nevertheless, such findings only emphasize the need for more detailed knowledge of lymphoreticuloendothelial function with particular reference to tumor-host interactions in human cancer.

SUMMARY

Hematoxylin and eosin and ammoniacal silver staining were employed to characterize lymph node patterns in cancer patients. The findings in an autopsy series were compared with those obtained in breast cancer cases at the time of surgery and with a series of noncancer cases. The lymph nodes tended to be responsive in the surgical series of cancer patients and degenerative in the autopsy cases. The lymph node patterns in the cancer cases were more similar to those which were seen in tuberculosis as contrasted with the response to acute infections.

The findings were discussed in terms of immunologic considerations and their implications to chemotherapy. Further studies of this type may shed light on some features of tumor-host interrelationships.

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RECURRENT LARYNGEAL NERVE INJURY DURING THYROIDECTOMY

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NEARLY 25 years have elapsed since Lahey (3) challenged the doctrine of the vulnerability of the recurrent laryngeal nerve—the conception that even the slightest injury from pressure or tension applied to the recurrent nerve may lead to paralysis. To prove his case, Lahey launched his large-scale experiment of routine dissection of the recurrent nerve at an early stage of the thyroid operation with the declared object of ensuring its safety. Although his results were impressive and won for him many supporters, the greater number of surgeons remained unshaken in their belief in the vulnerability of the nerve and the importance of avoiding any interference with this structure at operation.

Today, surgical opinion remains divided on this subject and probably will continue so until agreement has been reached on two fundamental questions: (1) whether dissection of the recurrent nerve, in view of its complicated anatomic course and variations, is a practical operative procedure and (2) to what extent this nerve can tolerate the ordinary trauma involved in its exposure at operation.

Attention is directed to these problems in this report which is based on the experience of 1,011 consecutive thyroid operations upon patients who were admitted to the David Lewis Northern Hospital, Liverpool, between January 1949 and December 1958 and for whom routine preliminary exposure of the recurrent laryngeal nerve was adopted. In dealing with patients with recurrent disease, each case was judged on its merits, and in some the laryngeal nerve was not exposed. This also applied to some cases of cysts and adenomas in which the laryngeal nerve was not at risk. These cases are not included in the series.

Preoperative treatment with antithyroid drugs followed by iodine was used for all thyrotoxic patients except for the mildest cases in which treatment was by iodine alone. Gas, oxygen, and ether by the endotracheal route were employed in the earlier cases and fluothane with appropriate relaxants in the later cases.

The technique described by Lahey (3) was followed with minor modifications. The recurrent nerve was clearly identified, but no attempt was made to lay it bare, and vessels running with it were carefully preserved; the nerve was not stripped in the manner of the dissecting room. Not infrequently, additional or complete exposure of the terminal portion of the nerve, as it lay between the trachea and the lateral lobe, was considered necessary, as, for example, in dealing with posterior marginal adenomas, in lobectomy, in some of the more radical operations for thyrotoxicosis, and when bleeding had to be controlled in this area.

Immediately before the wound was closed the anesthesia was lightened, and protective towels were arranged. The anesthetist then observed by direct laryngoscopy the normal limited range of symmetric abduction and adduction which occurs during quiet respiration. A blunt probe was next used to excite the laryngeal reflexes. This led to active and full adduction followed, after a pause, by full abduction. Occasionally, due to the depth of the anesthesia or to the effects of pressure by the intratracheal tube, one or both cords remained sluggish or immobile. A pause was made to allow these effects to wear off, and the examination was

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repeated. The nerve was assumed to be intact only when a completely satisfactory report was obtained. When either cord was suspect, the corresponding recurrent nerve was traced from below the level of the inferior thyroid artery to the cricothyroid junction in order to check its anatomic integrity and to exclude the possibility of its inclusion in a ligature or suture.

Every patient was examined in this way by direct laryngoscopy, but there were occasional instances in which a definite report on the action of the cords was not possible at the time; these patients were re-examined by indirect laryngoscopy within a few days of the operation. Repeated laryngoscopies were carried out on all patients who were found to have a cord lesion. Eighty per cent of the total number of patients have been re-examined by indirect laryngoscopy at varying periods after the operation.

In the course of this series, a patient was found upon laryngoscopy a few days after operation to have bilateral cord paralysis despite the fact that the cords had moved normally at the end of the operation. This situation clearly called for closer investigation, and all of the 338 subsequent patients in the series have been subjected to preoperative indirect laryngoscopy, direct laryngoscopy at the close of operation and early postoperative laryngoscopy usually within 7 to 21 days.

The diseases for which the 1,011 patients were operated upon were nontoxic colloid adenoma, 555; toxic adenoma, 221; primary thyrotoxicosis, 194; Hashimoto's thyroiditis, 12; nonspecific thyroiditis, 12; and carcinoma, 17. Bilateral exposure of the recurrent laryngeal nerve was carried out in 802 patients and unilateral exposure of the recurrent laryngeal nerve in 209.

Two deaths occurred during the course of this series but are not included in the figures. One was the result of coronary thrombosis; the other of cerebral thrombosis. Nonmalignant preoperative cord paralysis occurred in 6 patients who had had no previous operation. Four recovered. Postoperative cord paralysis was unilateral and permanent in 2; unilateral and temporary in 24; and bilateral, permanent in the right cord and temporary in the left cord, in 1. These figures include 1 permanent and 10 temporary cord lesions which occurred in the final 338 patients of the series.

LARYNGOSCOPY

The importance of preoperative laryngoscopy is illustrated by the 6 cases of preoperative paralysis discovered among our patients with benign adenomas who had not had a previous operation. Of these, 4 recovered and 2 were permanent. Unless preoperative laryngoscopy had been performed, these cases of paralysis would have been attributed to the operation.

In many clinics laryngoscopy is routinely performed at the end of operations, but the details of the actual procedures adopted vary considerably. We have found that direct laryngoscopy immediately before closing the wound has several advantages. The method can be used in every case and with no inconvenience to the patient; if a cord lesion is revealed, the corresponding nerve may be explored and, if the nerve is included in a ligature or suture, this may be removed; and if the nerve is found to be anatomically intact on exploration ultimate recovery is very probable.

It is obvious that a single postoperative examination of the cords may not tell the whole story and that for a complete record repeated examinations are necessary. The highest incidence of cord paralysis will be recorded when the patient is examined at the end of the operation, for this will include impairment of nerve function resulting from minor degrees of trauma from which a rapid recovery may take place. Very rarely a cord lesion first appears in the early postoperative period. The important distinction between temporary and permanent paralysis can be made only by later laryngoscopies, and, contrary to the view that after 6 months paralysis should be regarded as permanent, we have seen recovery after 12 and 15 months.

Late postoperative scar contraction has been cited by Crile and by Berry as a cause of vocal cord paralysis. Lahey regarded the risk as unimportant. We found no instance among 400 patients subjected to laryngoscopy more than 2 months after their operation.

DISCUSSION

Modern methods of anesthesia and preparation with antithyroid drugs, to ensure that all patients reach the operating theater in a nontoxic condition, have combined to reduce the risk of thyroidectomy, and technical procedures which formerly might have been considered inadvisable have been greatly facilitated. It must be admitted that preliminary exposure of the recurrent laryngeal nerve may prove both exacting and time-consuming, but with practice this is infrequent. We believe that the disadvantage of the vascular gland produced by the antithyroid drugs is more than compensated by the fact that the patient is nontoxic and, therefore, the additional time which is required to secure hemostasis is not of importance.

Recent anatomic research leaves no doubt that variation in the cervical course of the recurrent nerve is the rule rather than the reverse and that its course cannot be predicted. Techniques of surgeons who fail to recognize this are likely to lead to an increased incidence of recurrent nerve lesions. Certainly the time-honoured view that the recurrent laryngeal nerve lies snugly in the tracheo-esophageal groove in the lower part of the neck should be abandoned. Difficulties may arise at operation from (1) the frequency of anatomic variations in the course of the nerve; (2) replacement of the normal recurrent nerve by an aberrant or high division of the vagus; and (3) the presence of extralaryngeal branches. In addition to the ordinary anatomic variations, displacement of the recurrent nerve by adenomas and other conditions of the gland are by no means uncommon.

In the course of this series, despite the inconsistencies of the recurrent laryngeal nerve, outstanding difficulty in identifying this structure or its branches was exceptional. Our experience was similar to that recently recorded by Wade regarding the various anatomic situations which were found. From the purely anatomic standpoint, we were repeatedly impressed by situations in which a nonexposure technique might well have resulted in gross damage to the nerve. The facts that the right recurrent nerve was more inconstant in position than the left and frequently occupied a lateral or anterior position, sometimes in close proximity to the inferior thyroid veins, and that at a higher level the nerve often lay well forward on the lateral aspect of the trachea in relation to the ligament of Berry merely confirmed the experience of others.

The increased risk of injury when the nerve is displaced by adenomas was well illustrated by the posterior marginal adenomas which often lifted the nerve forward to lie between the adenoma and the main bulk of the lateral lobe—a situation which would invite disaster unless the nerve had been previously identified. In operation for retrosternal goiter, whenever conditions permitted, we first exposed the nerve in relation to the inferior thyroid artery before attempting delivery of the goiter, in order to assess its course in relation to the lower part of the tumor. Although, as a rule, left sided retrosternal adenomas usually displace the nerve medially against the esophagus and trachea, this displacement should not be assumed; on several occasions we found the nerve coursing obliquely upward on the lateral surface of the adenoma, and injury by traction during delivery of the adenoma or by ligation in mistaking the nerve for a vein appeared a very real danger.

Occasionally, when the right subclavian artery fails to develop in its normal position, an aberrant or high division of the vagus replaces the normal recurrent laryngeal nerve. Six examples of this anomaly occurred in our series, and in 2 of these the nerve was seen to be in two separate divi-

sions. This aberrant nerve is important to the surgeon for several reasons: the danger of ligation by mistaking it for an artery or a vein; the danger of including it with the ligature of the inferior thyroid artery, when they lie very close to each other; and the possibility of prolonged and fruitless search for the recurrent laryngeal nerve in the normal position, unless this anomaly is kept in mind.

The occurrence of extralaryngeal branches which leave the recurrent nerve at various levels below its entrance to the larynx and proceed to supply the laryngeal muscles is, of course, no new discovery. It was known to Wölfler who attributed incomplete postoperative paralysis of the vocal cord to damage of one or more of these branches. Lahey (4) recognized this anomaly, but on the whole it seems to have attracted surprisingly little notice in the surgical literature despite its very obvious importance in thyroidectomy. Anatomists, however, underline both the frequency of extralaryngeal branches and their liability to injury at operation. Rustad states that of the 200 nerves he dissected, 86 were divided nerve trunks with single or multiple branches and that, of these, 65 divided in areas frequently invaded during neck surgery. In view of the risk to extralaryngeal branches, he does not regard routine dissection of the recurrent laryngeal nerve as a practical procedure in the operating theater.

Our experience at operation provided good confirmation of these anatomic studies. The branches usually leave the main trunk at an acute angle and remain in fairly close proximity, although at times they pursue a complicated course in relation to the branches of the inferior thyroid artery. Their number varies; usually 2, but occasionally 3, and rarely 4 or more divisions are seen. We have found that it is of advantage to expose the recurrent laryngeal nerve at some distance below the inferior thyroid artery, that is, at a level below which branching rarely occurs, and then to trace the nerve upward so that any subsequent branches will be more readily recognized and preserved. The branches can be easily identified without resort to close dissection of the nerve, which is, of course, to be avoided. Despite Rustad's doubts, we have found that the recurrent laryngeal nerve and its branches can be sufficiently displayed, to establish their course in relation to any proposed resection of the gland and to vessels which may require ligature, without an elaborate dissection and with very little risk of significant injury.

VULNERABILITY OF THE RECURRENT LARYNGEAL NERVE

Crile postulated that, unlike the peripheral nerves which can withstand considerable trauma without resultant motor or sensory disturbance, the recurrent laryngeal nerve is so sensitive that any form of trauma, direct or by traction, is likely to result in cord paralysis. Lahey was strenuously opposed to this hypothesis. In England, the majority of surgeons still regard the recurrent laryngeal nerve as so sensitive to trauma that it should be avoided, if at all possible, at operation.

PERMANENT PARALYSIS

Two examples of permanent paralysis were due to division of the nerve during operations for primary thyrotoxicosis and thyroid adenoma. On both occasions the goiter was large and the operation difficult. In the third patient, at a secondary operation, the right recurrent laryngeal nerve was irreparably damaged in attempting neurolysis some 6 weeks subsequent to the original operation that was performed for adenomatous goiter.

We believe that this type of accident can always be avoided in the uncomplicated case, although occasionally excessive fibrosis and gross displacement of the nerve by tumors may prove formidable obstacles. Fortunately, radioactive iodine now provides a satisfactory alternative for the treatment of many of the difficult cases of recurrent disease.

TEMPORARY PARALYSIS

Of our 27 examples of cord paralysis, 24 proved to be temporary. Our experience indicates that, provided the anatomic continuity of the nerve is intact, the prospects of recovery are very good. Impressive series of cases have been published to support the view that the recurrent laryngeal nerve can withstand remarkably well the ordinary degree of trauma associated with its exposure during the thyroidectomy.

Inclusion of nerve by ligature. On two occasions the nerve was included in a ligature, being mistaken for a vein—one in relation to the inferior thyroid veins and one on the lateral surface of a retrosternal adenoma. The error was suspected and confirmed by direct laryngoscopy, and the nerve was not divided. After removal of the ligatures, recovery took place in 12 months and 4 months, respectively—striking testimony to the ability of the nerve to withstand quite severe injury. In a third case, direct laryngoscopy at the end of operation revealed a paralyzed cord. The nerve was therefore explored, and at its highest level it was found to be included in a suture passing between the gland and the trachea. The suture was removed, but the cord remained immobile. The patient could not be persuaded to submit to further laryngoscopy until 3 years after operation when the cord was found to be moving normally.

Minor direct injury and traction effects. It is often impossible to say with any certainty whether a temporary paralysis results from direct injury or from traction. Minor degrees of injury are to some extent inevitable during the actual exposure of the nerve, but every effort should be made to protect the nutrient vessels which accompany it in its course. At times, in this series, the nerve has been subjected to quite considerable trauma, as in some cases of recurrent goiter or thyroiditis, and no loss of function followed; but we must attribute to trauma the remaining 21 examples of temporary paralysis. We found no significant difference in the incidence of cord lesions among the three main types of goiter—nontoxic adenoma, toxic adenoma, and primary thyrotoxicosis.

Our records indicate that operation for retrosternal goiters involved more than average risk of cord paralysis, especially when we were unable to identify the nerve before delivery of the tumor from the thorax. It seems probable that traction rather than direct trauma is responsible for many of these lesions, as the nerve was often displaced by the tumor into a position which rendered it particularly liable to traction injury during delivery.

Although considerable retrolaryngeal extensions of the upper pole, at times bilateral and meeting in the mid-line behind, were by no means rare, these operations were not followed by nerve lesions. It may be noted that in all such cases the infrahyoid muscles were freely divided before delivery of the poles was attempted. This division undoubtedly reduced the risk of traction injury. Crile condemned all attempts at delivery of the upper poles, as he regarded the risk of nerve paralysis from tension as prohibitive.

Paralysis developing in the early postoperative period. Occasionally unilateral or bilateral cord paralysis, perhaps with severe stridor, results from clot retention in the wound during the early postoperative period. Provided that, at reoperation to evacuate the clot, the surgeon takes the obvious precaution of identifying the recurrent laryngeal nerve before applying forceps or ligatures to check bleeding, recovery from the paralysis may be anticipated, although occasionally tracheotomy proves necessary in the meanwhile.

Paralysis may also arise soon after operation from causes other than clot retention and is by no means confined to patients for whom an exposure technique has been employed. Williams has recorded 7 examples among 100 operations in which the recurrent laryngeal nerve was not exposed. Two of these proved permanent. Little is known about this type of paralysis, and the subject

deserves further investigation especially with regard to prognosis. Edema and fibrosis have been held responsible, but the lesion is probably basically the result of ischemia of the nerve, and recovery presumably depends on the re-establishment of blood supply. The results of physiologic experiments lend some support to this view. This complication is fortunately of rare occurrence, but the onset is unpredictable and, if unfortunately both nerves are affected, a dangerous situation requiring tracheotomy may arise.

We had 4 examples, of which 1 was bilateral. This patient, aged 72 years, had extensive cervical and bilateral retrosternal adenomas with marked obstructive effects. Both recurrent nerves were exposed up to the level of the cricothyroid joint but only after delivery of the retrosternal masses. The cords moved normally at the end of operation, and for the first few days all was well. Then a gradually increasing stridor developed, and laryngoscopy revealed bilateral abductor paralysis. Tracheotomy was suggested, but the patient declined. Six weeks later the right side of the neck was explored. Very extensive scar tissue had developed, and the right recurrent nerve was irreparably damaged in attempting to free it. This, however, relieved the adductor spasm of the right cord with some improvement in breathing. Recovery of the left cord was slow but progressive. Twelve months later, abduction was still limited, but laryngoscopy 2½ years after operation revealed full movement of the left cord and a fixed right cord.

There are points of interest in this case. Normal movements of the cords had been observed after operation; tracheotomy, as originally suggested to the patient, might well have tided her over until the cords recovered; and the decision to explore the nerve at the sixth week was obviously premature, as judged by the subsequent recovery which took place in the left recurrent nerve.

The remaining 3 cases were discovered at follow-up laryngoscopy during the second week after operation. Recovery in 2 cases took place within 8 weeks. The third patient did not report for further laryngoscopy until 7 months after operation, at which time the cord was discovered to move normally. In each of these 3 cases, there was some weakness of the voice during the early postoperative period but this, however, gradually disappeared.

CONCLUSION

A total of 28 cord lesions that followed 1,011 operations in which one or both recurrent laryngeal nerves were deliberately exposed provides little support for Crile's vulnerability theory. On the contrary, the risk appears to be of the order that might be expected with any peripheral nerve of corresponding size. Occasional temporary lesions appear inevitable, but permanent paralysis which results from gross lesions of the nerve, such as division or permanent ligature, can almost always be avoided. The risk of paralysis developing in the early postoperative period is slight but cannot be discounted and, at present, the prognosis must be regarded as uncertain.

SUMMARY

In a series of 1,011 thyroidectomies in which an exposure technique was used for the recurrent laryngeal nerve, there were 28 examples of vocal cord paralysis. Of these, 3 proved to be permanent. In spite of the complicated anatomic course of the nerve and its branches, preliminary exposure of these structures is undoubtedly a practical surgical procedure.

Direct laryngoscopy should be performed routinely at the completion of the operation.

Gross lesions involving anatomic division of the nerve produce permanent paralysis, but by use of an exposure technique such an accident can almost always be avoided. Minor degrees of injury, such as may be expected in a carefully conducted operation, are usually well tolerated, but, if paralysis follows, it will probably prove temporary.

Paralysis due to ligature or suture usually ends in recovery, provided that the material is removed. Very rarely paralysis first develops in the early postoperative period. Until more cases have been studied a guarded prognosis should be given, although probably recovery will follow. Late postoperative paralysis resulting from scar contraction appears to be very rare.

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FETAL BLOOD STUDIES

XVIII. Supplementary Observations on the Oxygen Pressure Gradient Between the Maternal and Fetal Bloods of Humans

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THE OBSERVATIONS to be presented here on the oxygen pressure gradient that exists between the maternal and fetal bloods of the human, separated by the three tissue layers that form the hemochorial placenta, are in the nature of a supplement to results published earlier (1). In that article data were presented on the oxygen capacity, oxygen content, percentage saturation, and estimated oxygen pressure of samples of blood drawn from each of the three placental vessels—the intervillous space, umbilical vein, and umbilical artery. From these data the differences in oxygen pressure across the human placenta were estimated.

It is important to state that in the first report the *p*H of maternal and fetal blood was disregarded. Also, the oxygen dissociation curves of maternal and fetal blood—used to estimate oxygen pressure—were assumed to be correct.

In an attempt to increase the accuracy of estimating oxygen pressure, two studies were designed. In the first a set of maternal and fetal oxygen dissociation curves were constructed at known *p*H (2). In the second, samples of blood were obtained from the three major placental vessels and were analyzed for oxygen content, oxygen capacity, and *p*H. With these data we then were able to refer a percentage saturation

$$\left(\frac{\text{oxygen content}}{\text{oxygen capacity}} \times 100\right)$$

at a known *p*H to its appropriate dissociation curve. When this information was obtained, it was considered advisable to reinvestigate the subject of the oxygen pressure gradient across the human placenta.

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MATERIALS AND METHODS

The 4 patients upon whom observations were made were all delivered by cesarean section. All 4 of the subjects were considered normal, and the operative procedures were performed because of previous cesarean sections. In 1, delivery was complicated by severe spinal hypotension (referred to in Table I and in the text as "abnormal"). The duration of pregnancy, based upon the patients' menstrual data, varied from 37 to 39 weeks.

The procedures employed to obtain the intervillous space and the umbilical vessel samples as well as the method of measuring oxygen content and capacity have been reported previously (1). The only additional evaluation was the measurement of the *p*H in each sample. This was accomplished by driving a portion of each blood sample into a centrifuge tube and under oil; after centrifugation, the plasma sample was collected and the *p*H measured on a Beckman *p*H meter standardized with a buffer of known hydrogen ion concentration. The determinations were corrected to 38 degrees C. by using Rosenthal's factor.

RESULTS

All the data are presented in Table I. It can be seen that the oxygen pressure gradient in normal pregnancy equals approxi-

TABLE I.—DATA OBTAINED ON BLOOD SAMPLES DRAWN FROM PLACENTAL VESSELS

Type pregnancy	*Placental vessel*	*Oxygen capacity, vol. per cent*	*Oxygen content, vol. per cent*	*Per cent saturation*	*pH at 38°C.*	*Estimated pO_2, mm. Hg*	*Oxygen gradient, mm. Hg*
Abnormal	Intervillous space	16.5	9.5	57.5	7.33	32.0	10.0
	Umbilical vein	22.9	9.7	42.3	7.29	22.0	
Normal	Intervillous space	17.4	16.0	91.9	7.41	53.0	
	Umbilical vein	22.8	16.2	71.0	7.41	31.0	29.5
	Umbilical artery	22.8	6.1	26.7	7.42	15.0	
Normal	Intervillous space	11.1	9.3	83.7	7.36	44.5	
	Umbilical vein	18.6	12.3	66.1	7.36	30.0	22.0
	Umbilical artery	18.6	5.7	30.6	7.34	16.0	
Norma	Intervillous space	14.9	12.2	81.8	7.40	42.5	
	Umbilical vein	21.0	11.0	52.3	7.33	24.0	21.8
	Umbilical artery	21.0	7.2	34.2	7.29	18.0	

mately 24 millimeters of mercury (range 21.8 to 29.5); in the 1 abnormal case, however, the pressure difference is only 10 millimeters of mercury.

The major difference demonstrated by the data seems to be that the intervillous blood is more unsaturated in abnormal pregnancy. Whereas the average intervillous space pressure equals 47.0 millimeters of mercury in the normal individuals, in the abnormal the value is only 32.0 millimeters of mercury—a difference of 15.0 millimeters of mercury. On the other hand, the data on umbilical vein blood are similar in the two groups, for in the normal the average pO_2 is 28.0 millimeters of mercury, while in the abnormal it equals 22.0 millimeters of mercury.

DISCUSSION

There are obvious sources of error in the method used for the estimation of the average oxygen pressure difference between the maternal and fetal bloods in these 4 cases and in the 14 previously reported. However, they would not appear to invalidate the conclusion that the values obtained are of the right order. If the data are representative of the conditions in utero, then it may be inferred that the oxygen pressure gradient across the placenta is of the order of 24.0 millimeters of mercury; and further, that the gradient is altered appreciably in abnormal pregnancy. It is tempting to associate the reduced gradients in clinically abnormal pregnancies with a diminution in oxygen transfer to the fetus, but until other aspects of placental oxygen transfer are evaluated, it would seem wise to hold such feelings in abeyance.

SUMMARY

By using data recently obtained, estimates have been made of the difference in the oxygen pressures of fetal and maternal human blood as they pass through the placental capillaries. Data from 3 normal patients at term were analyzed; the oxygen pressure difference averaged 24.0 millimeters of mercury. In 1 abnormal patient the pressure difference was only 10 millimeters of mercury.

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EDITORIALS

REQUIREMENTS OF ADEQUATE CANCER OPERATION ON THE COLON, RECTUM, AND ANUS

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WHAT ARE the requirements of an adequate operation for cancer of the colon, rectum, and anus? A quick reply to this question might be, "One which cures the patient"; but that would be an ill-conceived and far oversimplified answer.

The mere fact that one is dealing with a malignant lesion of the colon, rectum, or anus is not justification for a stereotyped technical procedure. If, before and at the time of operation, experienced judgment considers the lesion resectable; if it is resected and the pathologist confirms, so far as he can, the hope that the resection was sufficiently extensive; if thorough exploration with the hand is carried out; and if biopsy of suspect tissue, as for instance in the liver, is performed and no distant metastatic lesion is found—then the surgeon is justified in classifying the procedure as nonpalliative.

If local involvement is too extensive to permit removal of all the malignant tissue, or if a distant metastatic lesion is found, then even though primary resection is done to relieve obstruction, to retard growth, or to remove the main feeder of metastasis, the procedure must be classified as palliative.

It is already apparent that a multitude of negatives are implied in an answer. And yet, quite unexpectedly, one encounters a patient who defies all rules and humbles prognostic judgment that seemed infallible, particularly when a bad outlook had been predicted.

As a case in point is the history of a man operated upon in 1937, at 23 years of age for an obstructing, annular, ulcerating, and fixed carcinoma, grade 1, of the upper portion of the rectum and the rectosigmoid. A palliative, double-barrel sigmoid colostomy was recommended, with no conviction of helpfulness, to be followed by roentgen and radium therapy. This was carried out. The patient received the last such treatment in September 1937 and was last examined in August 1938. In 1957, in answer to a follow-up questionnaire he stated he was in excellent health and had had no illnesses since 1938, except for an occasional cold and other minor illnesses. The patient has since reported that he is well and his home physician is considering re-establishing continuity of the bowel.

A review of purely palliative colostomy operations has revealed that it extends survival by an average of only 1 month, and in practically all instances a pathetic month. Instead of colostomy, it is better to recommend a low residue, later a minimal residue, and finally a nonresidue diet.

Unless so much of the liver is involved as to make such a procedure useless, the primary growth should be resected when possible and an end-to-end anastomosis performed in one stage, without concomitant colostomy.

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When palliation with fulguration, roentgen therapy, and irradiation cannot be carried out adequately for lesions of the anus, rectum, and rectosigmoid, a sigmoidostomy rather than transverse colostomy should be performed because the sigmoid is closer to the involved portion of the bowel and the amount of mucous drainage is cut down.

With rare exception, regardless of the extent of resection of the abdominal portion of the colon, it can and should be done in one stage.

The question of an adequate nonpalliative operation for a lesion of the colon relates to the extent of the resection for a given lesion in a given location. A variety of suggestions ranging from colectomy and ileoproctostomy to much more moderate resections to remove the growth have been expressed on this subject.

A surgeon tends to practice technically what he has been taught. Generally, he is well able to defend what he does and to be destructively critical of other surgeons who do more extensive or less extensive resections. In this situation as in so many similar ones, it is a good idea to be a "middle-of-the-roader," neither overdoing nor underdoing the resection.

First, one must be certain of the diagnosis. Extensive rectum-sacrificing resections have been done for an endometrioma; a combined abdominoperineal resection has been done for a lesion for which sigmoidoscopic fulguration should have been advised. It should create an extremely uncomfortable feeling to find that an extensive resection has been performed in the case of a benign lesion.

It is important to be certain of blood supply to the colon and to be aware of the variations in blood supply. The right colic artery should be ligated early, before a growth in the right portion of the colon is manipulated. The middle colic artery should be ligated for a growth in the transverse colon or splenic flexure, and the left colic, or inferior mesenteric artery, should be tied for lesions in certain parts of the descending colon and sigmoid.

For a resectable lesion in which the lower border lies within 6 centimeters of the dentate margin, or within 9 centimeters of the anal verge, a one stage low anterior resection and end-to-end sigmoidoproctostomy is preferable. This operation can be performed with the proper, long instruments. The only obstacle which can prevent this operation technically is obesity. It is preferable not to perform concomitant colostomy. Mortality is in the 6 per cent range and morbidity, in terms of hospitalization, is about 2 weeks. In the controversial group of lesions, which lie 6 to 14 centimeters above the dentate margin (9 to 17 cm. from the anal verge), the 5 year survival rate in nonpalliative resections has recently been found to be 61.3 per cent, and the 10 year survival rate to be 52.6 per cent. These figures compare favorably with those for survival after one stage combined abdominoperineal resection, and the figures for incidence of residual or recurrent carcinoma compare favorably also. Therefore, it would appear that low anterior resection with end-to-end anastomosis is an adequate surgical procedure and, from the patients' standpoint, a very acceptable one. The anus becomes very important when it may be lost.

The one stage combined abdominoperineal resection with wide resection of gland-bearing tissue, including the inguinal glands for anal lesions, may be considered an adequate operation.

When surgical mortality is kept within acceptable limits and hospital and subsequent morbidity is low, when life is productive and pleasant and—with due allowances made—5 and 10 year survival rates are high, then an operation can be said to be adequate. The good surgeon is always questioning his own procedures, is always trying to individualize his patients, and to improve his treatment. He seeks for the patient the operation and the result he would wish for himself—this is an adequate procedure.

POTENTIAL TREATMENT OF CANCER BY ELECTROMAGNETIC HEATING

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THE THERAPEUTIC ATTACK on cancer is being made along several lines. Surgery is still the major weapon. Various forms of radiation, roentgen rays, radium, and isotopes are probably second. The effects of various hormones have shown results in special situations. Cancericidal drugs are being developed and evaluated. The enzyme systems are also being given attention. However, it seems to us that an entirely different line of attack is warranted.

Probably the commonest means of controlling animal or biologic growth is by a change in temperature. In nature, the sharp limitation of plant and tree growth caused by a relatively minor mean temperature change is seen most dramatically on the sides of high mountains or in the Grand Canyon of Arizona. Such effects are well known to agriculture. In general, most plants and animals can withstand relatively low temperatures for a much longer period than they can tolerate a comparable rise of temperature above the mean.

A rise in temperature of the plant or organism is lethal if prolonged for sufficient time. A common use of this method is the pasteurization of milk. This accomplishment depends on an elevation of temperature for about 30 minutes and would not be effective if the exposure were shorter.

The amount of heat or temperature rise required to produce death of cells, either malignant or normal, within the intact mammalian body is no doubt different for various cells and tissues. There is little general knowledge of this important field. One of the best controlled studies was that of Moritz and Hendriques who, in reporting on the effect of heat on porcine and human skin, showed that "the time required to produce irreversible injury bore an inverse relationship to temperature." Thus, surface exposure for 3 hours at 45 degrees C., 0.4 minute at 55 degrees C., or 0.1 second at 100 degrees C. were the minimal times required to produce transepidermal necrosis. Also, when cutaneous hyperthermia was prolonged 40 to 60 per cent of the minimum time required for the production of transepidermal necrosis, "it resulted in a severe and pathologic vascular reaction with edema and cyanosis and one which persisted for days rather than for minutes or hours." The flow of blood through the capillaries was slowed. Within 1 hour after the onset of a vascular injury of this grade, the water content of the dermis was increased by as much as 100 per cent.

The virus producing hepatitis is killed by exposure of serum to room temperature for 6 months, whereas it simply seems to be preserved by low temperatures. Is it possible that the agent causing cancer, which some think is a virus, could be destroyed in a similar manner?

Dr. Coley's vaccine is still under investigation, and there are many cases of proved cures or long-time arrest of malignant growths which were treated in this way. An essential part of this treatment is a strong febrile reaction.

A recent report by Medal and associates indicates that in the intact animal exposed to an electromagnetic field of 1,500,000 volt-amperes with a magnetic field strength of 450 oersteds and having a frequency of 1.1 kilocycles per second it is possible to cause local necrosis in tissue which contains 0.005 gram of magnetic particles measuring .02 to .1 micron in diameter. The particles are heated by hysteresis. This is a form of

magnetic friction and acts independent of individual particle size. The hysteresis heating of the magnetic particles is accompanied by relatively slow heating of the normal tissues. The tissue heating is due to eddy current heating which occurs when any conductive material is placed in an electromagnetic field, and it increases with the diameter of the material. This eddy current heating is most commonly seen in medicine when inductothermy is used. The inductotherm usually operates at a frequency of 13 megacycles per second or higher, in contrast to the 1.1 kilocycle frequencies used here.

Medal has developed a thermister which will record temperature to 0.5 degrees C. within different viscera in the intact animal at the time of exposure to these strong electromagnetic fields.

Preliminary studies show that the various viscera—liver, kidney, stomach, colon—heat at different rates when so treated if no target material is present. Unreported studies in the live animal indicate that a rise of liver temperature from 44 to 46 degrees C. for a short time does not result in irreversible liver changes either on microscopic section or by several liver function tests.

These studies suggest that it will eventually be possible to raise the temperature in specific internal organs, without lethal effects, by properly constructed coils and proper radio frequencies even without target material. The heating will be due more and more to the dielectric effect and less and less to eddy current.

Thus, cancer, even if it is not due to a virus, should succumb to such elevated temperatures since it is accustomed to growing in a very restricted thermal environment. However, it would seem likely that the temperature effect might be enhanced by the systemic use of some of the other agents now used, most likely the hormones, enzymes, or cytotoxic drugs.

New equipment has been designed and is being built to carry out detailed studies in sizeable experimental animals. The effects of temperature elevation on the various viscera and on experimental tumors can be accurately studied since the temperature differential can be obtained by using the target material if it is needed.

Regardless of the etiologic agent causing cancer, this approach to the control of malignant growth by localized elevation of temperature certainly warrants intensive investigation.

THE SURGEON AT WORK

A TECHNICAL AID IN BILATERAL INGUINAL HERNIORRHAPHY IN INFANTS AND CHILDREN

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WITH INCREASING FREQUENCY, today's surgeon advises prompt repair of inguinal hernias in children, regardless of age. Improved anesthesia and proper intravenous support make even the youngest infant a reasonably safe candidate for this type of surgery.

Almost all of these hernias are of the indirect type, and the great majority occur in males. Because a high percentage of infants and children with an apparent unilateral inguinal hernia are eventually found to have involvement of the opposite side, many surgeons advocate exploration of the contralateral side as a routine. It has been estimated by Gilbert and Clatworthy that 60 per cent of children with apparent unilateral inguinal hernia will show involvement of the unsuspected side as a result of such exploration. It would seem, then, to be good surgical practice to explore both inguinal regions in an otherwise healthy child even though only one hernia can be demonstrated.

One of the difficulties in performing herniorrhaphy in infants and young children is that of identification of the peritoneal sac. The various structures are not only small but very delicate and are easily torn or injured by manipulation. The vas and its accompanying blood vessels are all too frequently subject to injury in the process of finding and isolating the sac.

METHOD

The following simple method was used in 7 cases and was found to be of distinct value in identifying the second sac in bilateral inguinal hernia repair in infants (Fig. 1).

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The usual procedure for hernial repair is carried out on that side which either shows a definite rupture or is the larger of a demonstrable bilateral hernia. In so doing, as soon as the sac has been isolated and opened, a small No. 12 soft French catheter is passed through the sac into the peritoneal cavity in the general direction of the opposite inguinal region. The operating table is then placed in slight Trendelenburg position, and about 5 cubic centimeters of air are injected through the catheter into the peritoneal cavity with a Dakin syringe. The catheter is then withdrawn and the usual repair of the hernia completed.

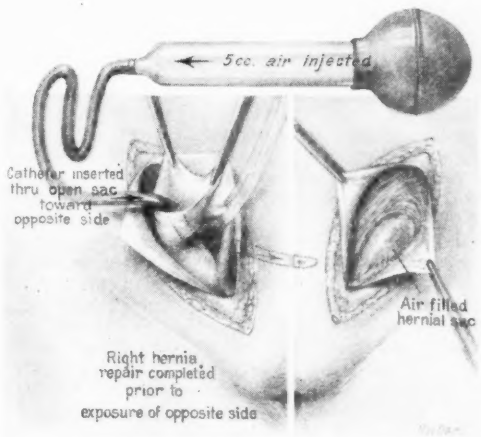
5cc. air injected
Catheter inserted thru open sac toward opposite side
Air filled hernial sac
Right hernia repair completed prior to exposure of opposite side
a
b

FIG. 1. a, Air injected into peritoneal cavity when sac is first opened to be followed by usual repair. b. After exposure of second side, an air filled bleb of peritoneum denotes exact location of the sac.

The opposite inguinal area is then explored, and after dividing the external oblique fascia identification of the cord is made. Upon close inspection of the upper end of the exposed segment of cord near the internal ring, one may expect to find a small, air-filled bleb of peritoneum indicating the exact location of the hernial sac. Sometimes the sac may contain many small air bubbles mixed with peritoneal fluid, and is easily recognized as such. Considerable time is thus saved as well as the avoidance of unnecessary exploration and dissection. The sac is then exposed, and the hernia repaired as on the opposite side.

CASE REPORT

The following case represents a typical instance in which this procedure proved most useful.

J. C., age 2 months, when first seen had a bulge in the right groin, descending into the scrotum, which was unmistakably a congenital inguinal hernia. The swelling was first noted shortly after birth, and the baby cried every time the swelling protruded. On one occasion, approximately 2 weeks earlier, a similar but smaller swelling was noted in the left groin.

Upon examination, this healthy-appearing 2 month old male infant was found to have a reducible inguinal hernia on the right side. No hernia or dilated ring could be determined on the left side. Both testes were normal in size and position.

The infant was hospitalized on 3 January 1959, and on the following day the right inguinal hernia was repaired. The technique described was employed, and, upon exploring the left inguinal area, after division of the external oblique fascia, a sac of peritoneum filled with air, about 1 centimeter in diameter, was immediately found just outside the internal ring. The sac was opened and the hernia repair completed without difficulty.

SUMMARY

In more than 60 per cent of infants and children with demonstrable unilateral inguinal hernia, a hernia subsequently developed on the unsuspected side. It would seem, therefore, good surgical practice to expose both inguinal areas in otherwise healthy children. The introduction of a small amount of air into the peritoneal cavity upon repair of the first side and placing the table in slight Trendelenburg position aid in identifying the remaining sac quickly and safely and, thus, minimize the amount of exploration and dissection required.

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1. Gilbert, M., and Clatworthy, H. W., Jr. Inguinal hernia and hydrocele in infancy and childhood. Am. J. Surg., 1959, 97: 255-259.

THE LIMITATIONS OF THE INTRAVENOUS PYELOGRAM AS A TEST OF RENAL FUNCTION

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THE LIMITATIONS of the use of intravenous pyelograms as an indicator of renal function are emphasized in this report. At the present time, pyelographic evidence of satisfactory function of an anatomically normal kidney is accepted as sufficient indication of life-sustaining ability to permit removal of the opposite kidney. The statement that good, early roentgenographic visualization of the calyces and pelvis of a kidney after intravenous injection of a contrast medium implies comparatively normal renal function is common. The tendency to employ this method in evaluating renal function to the exclusion of more accurate methods persists despite the awareness that varying degrees of visualization of the urinary tract are possible in patients in whom there is unequivocal evidence of bilateral impairment of renal function. The intravenous pyelogram, as performed today, represents the radiographic end result of the administration of one of a rather impressive number of organic iodides, available in varying concentrations, given in indefinite dosages, and excreted by a renal mechanism which in many instances has not been determined accurately. Under these circumstances, it seems inevitable that kidneys shown by more quantitative means to be functionally impaired should occasionally appear pyelographically normal. In reviewing the renal functional status of patients recently subjected to intravenous pyelography the following examples are presented to support this contention.

CASE REPORTS

CASE 1. F. B., a 67 year old white male, was admitted to the hospital with complaints of pain on the right side of the chest radiating into the right axilla of 24 hours' duration and moderate exertional dyspnea of 3 months' duration. The only urinary complaints were a recent decrease in the force of stream and a recent onset of nocturia, 1 to 2 times a night. Two years prior to this admission blood urea nitrogen was 31 milligrams per cent. Other tests of renal function revealed comparable impairment at that time. As a result of these tests, a diagnosis of chronic nephrosclerosis with renal insufficiency had been made. Results of an intravenous pyelogram performed with 50 per cent miokon®[1] at that time was negative. Physical examination on admission revealed a thin, emaciated elderly male whose blood pressure was 176/98. Examination of the chest disclosed findings typical of pulmonary emphysema. Examination of the abdomen revealed a liver palpable to 5 centimeters below the right costal margin.

Urinalysis on admission revealed an acid urine with a specific gravity of 1.008, no protein or reducing substances, occasional leucocytes, and many hyalin casts per high-power field. The blood urea nitrogen on admission was 52 milligrams per cent; a repeat determination 1 week later revealed that it had increased to 70 milligrams per cent. Phenolsulfonphthalein excretion was 4 per cent in 15 minutes and 4.5 per cent at 30 minutes, a total in 30 minutes of 8.5 per cent. Despite this degree of impairment of renal function, the intravenous pyelogram (Fig. 1) performed with an unidentified contrast medium, presumably diatrizoate sodium, showed prompt excretion and good concentration of this medium.

CASE 2. H. K., a 61 year old white male, was admitted to the hospital because of shortness of breath, substernal pain, and dizzy spells present for several months. There were no urinary symptoms.

Physical examination revealed a well developed, apprehensive patient in no acute distress. Blood pressure was 190/90; pulse rate was 66 per minute; and respiratory rate was 30 per minute. Fundoscopic examination showed a mild arterial tortuosity with an arteriovenous ratio of 1 to 3. The chest was increased in its anteroposterior diameter. Scattered moist rales and rhonchi were present. The left border of the heart was percussed at the anterior axillary line in the fifth intercostal space. There was a grade II systolic murmur heard at the apex. Examination of the abdomen and extremities disclosed no abnormalities.

Urinalysis revealed an acid urine with a specific gravity of 1.002 containing a trace of albumin, no reducing substances, 1 to 3 leucocytes and an occasional erythrocyte per high-power field. The blood urea nitrogen was 57.8 and 24.7 milligrams per cent. Concentration to dilution ability was 1.013 to 1.003. Phenolsulfonphthalein excretion was 7 per cent in 15 minutes, and 14 per cent at 30 minutes, a total of 21

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[1]A brand of sodium diprotrizoate.

FIG. 1.

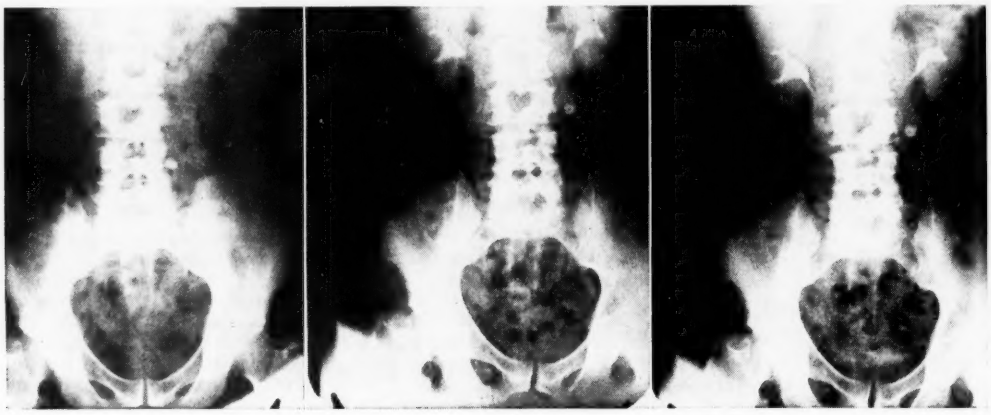

FIG. 2.

FIG. 1. Case 1. Intravenous pyelograms taken at 5, 10, and 15 minute intervals show good concentration and prompt excretion of contrast medium in patient with impaired renal function of at least 2 years' duration. Blood urea nitrogen was above 50 milligrams per cent at time pyelograms were made.

FIG. 2. Case 2. Intravenous pyelograms show negative findings despite impaired concentration to dilution ability, phenolsufonphthalein excretion, and urea clearance, as well as elevated blood urea nitrogen. Pyelograms of kidney, ureter, and bladder were taken at 5 and 15 minute intervals.

per cent in 30 minutes. Urea clearances repeated twice were 23 and 29 per cent of normal. A diagnosis of benign nephrosclerosis was made. Despite the reduction in renal function, an intravenous pyelogram performed with an unidentified contrast medium, presumably 50 per cent diatrizoate sodium (Fig. 2), revealed "prompt bilateral excretion of dye with good concentration." The intravenous pyelogram was made within 3 days of admission.

CASE 3. J. B., a 69 year old negro male, was admitted to the hospital because of shortness of breath of 1 week's duration. On physical examination, the only abnormalities were a surgical absence of the left breast and a marked increase in the anteroposterior diameter of the chest. In addition, hyperresonance was noted on percussion of the chest; breath sounds were distant. Routine urinalysis was reported as showing a specific gravity of 1.005; an occasional leucocyte was noted. Urinalysis showed no reducing substances and no albumin. Blood urea nitrogen determinations were reported as 30 milligrams per cent. An intravenous pyelogram (Fig. 3) showed prompt excretion of the contrast medium bilaterally. Ptosis of the right kidney was noted.

CASE 4. W. H., a 69 year old white male diabetic, was admitted to the hospital with complaints of severe

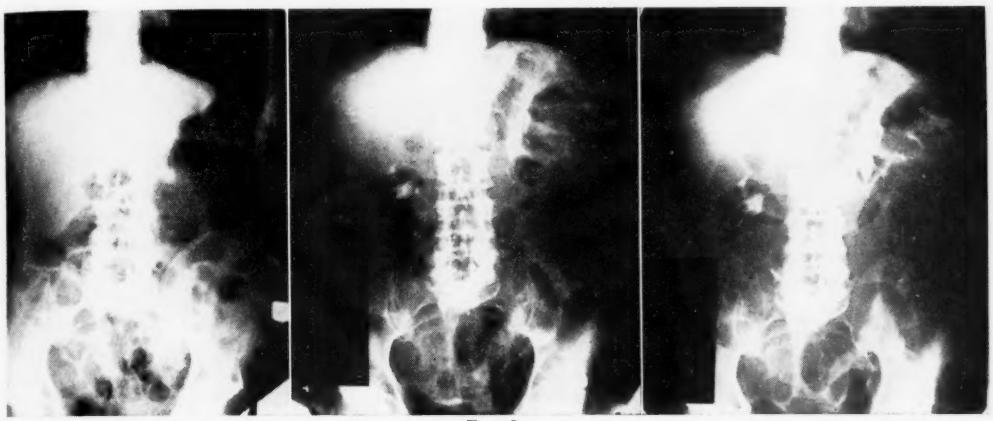

FIG. 3.

FIG. 4.

FIG. 3. Case 3. Prompt bilateral excretion of dye with good concentration in patient with persistent moderate elevation of blood urea nitrogen levels. Pyelograms of kidney, ureter, and bladder were taken at 5 and 10 minute intervals.

FIG. 4. Case 4. Intravenous pyelograms of patient with mild to moderate impairment of renal function show essentially negative findings. Pyelograms of kidney, ureter, and bladder were taken at 5 and 10 minute intervals.

exertional dyspnea, orthopnea, and generalized weakness of 1 month's duration and of 6 episodes of syncope during the past year.

On physical examination blood pressure was 108/60, pulse rate 150 per minute, and respiration 16 per minute. Upon examination of the chest, the only abnormality noted was a grade II systolic murmur over the aortic area radiating down the left sternal border to the apex. On examination of the abdomen, the liver edge was palpable 10 centimeters below the right costal margin. No other significant abnormalities were disclosed by the examination. An electrocardiogram indicated an atrial flutter with a 2 to 1 heart block. The diagnosis of rheumatic heart disease, inactive, with rheumatic valvulitis of the aortic valve, inactive, and aortic stenosis was made.

During the course of hospitalization, laboratory studies revealed impaired renal function. Urinalysis showed a specific gravity of 1.012, a trace of albumin, no reducing substances, 6 to 9 leucocytes, and an occasional granular cast per high-power field. The blood urea nitrogen level varied from a high of 44 milligrams per cent to a low of 24 milligrams per cent during hospitalization. Concentration to dilution ability was 1.013 to 1.010 on 1 occasion, and it showed a maximum concentrating ability of 1.019 on another. Phenolsulfonphthalein excretion was determined on 2 occasions. Initially, a total of 22.5 per cent of the dye was excreted in 30 minutes, only 6 per cent being present in the 15 minute specimen. A second test per-

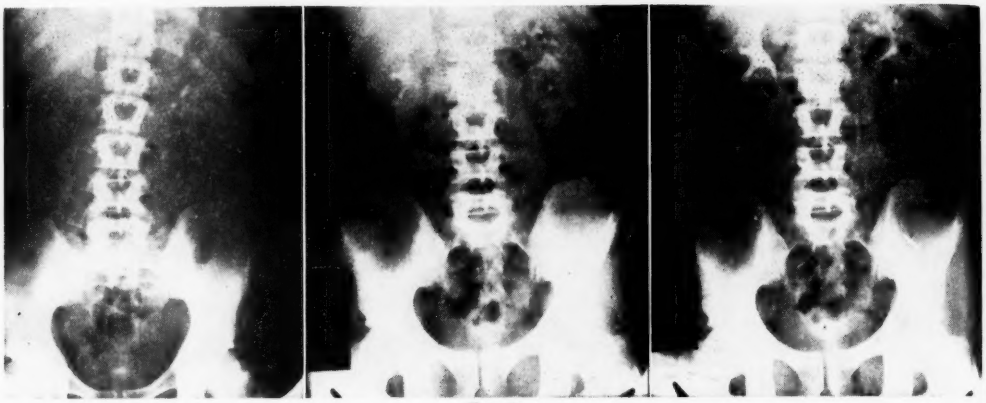

FIG. 5.

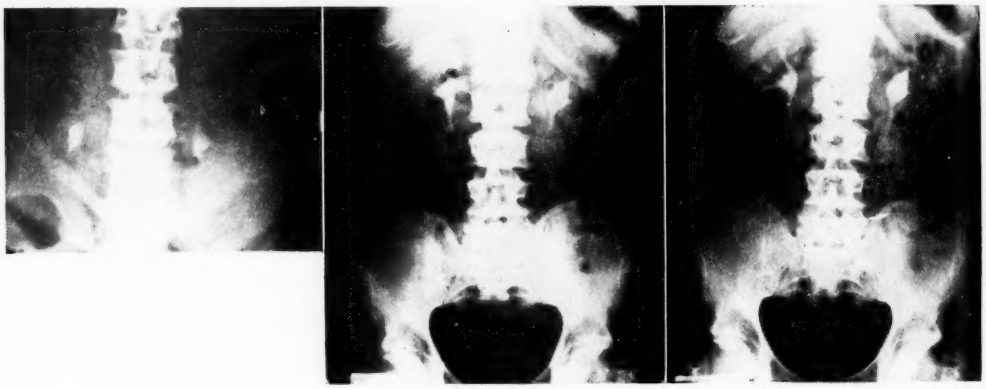

FIG. 6.

FIG. 5. Case 5. Intravenous pyelograms show essentially negative findings even though acute proliferative glomerulonephritis was the finding upon biopsy of the right kidney 2 days later. Diagnosis was confirmed at second biopsy.

FIG. 6. Case 6. Intravenous pyelograms of patient with marked impairment of renal function of 10 years' duration taken at 5, 15, and 30 minute intervals. Blood urea nitrogen at pyelography was 25 milligrams per cent, creatinine 3+ milligrams per cent.

formed after the blood urea nitrogen level had dropped showed a total of 33 per cent of the phenolsulfonphthalein excreted in 30 minutes, with 15 per cent being present in the 15 minute specimens. These tests indicated a mild to moderate degree of impairment of renal function. An intravenous pyelogram (Fig. 4) performed when the blood urea nitrogen was 28 milligrams per cent was reported as showing "prompt bilateral visualization, good concentration." The exact nature of the contrast medium was not recorded although it was presumably 50 per cent diatrizoate sodium.

CASE 5. A. C., a 40 year old white male, was admitted to the hospital because of malaise and fatigue of 3 months' duration. These complaints persisted after what seemed to have been an upper respiratory tract infection. Just prior to admission, the patient noticed a generalized red, blotchy skin eruption. In the review of systems the patient related that he had had a chronic dermatitis on his hands and feet for 11 years. This had been diagnosed by several dermatologists as erythema multiforme.

On physical examination, the patient was a small, well-nourished white male who did not appear acutely ill. Blood pressure was 130/88, pulse 88 per minute, and respirations 20 per minute. Examination of the integument revealed a generalized erythematous vesiculopapular eruption. Excoriated, scaly, erythematous lesions were noted over both hands and over both lateral malleoli. The remainder of the physical examination revealed no significant abnormality.

Laboratory studies revealed the hemoglobin to be

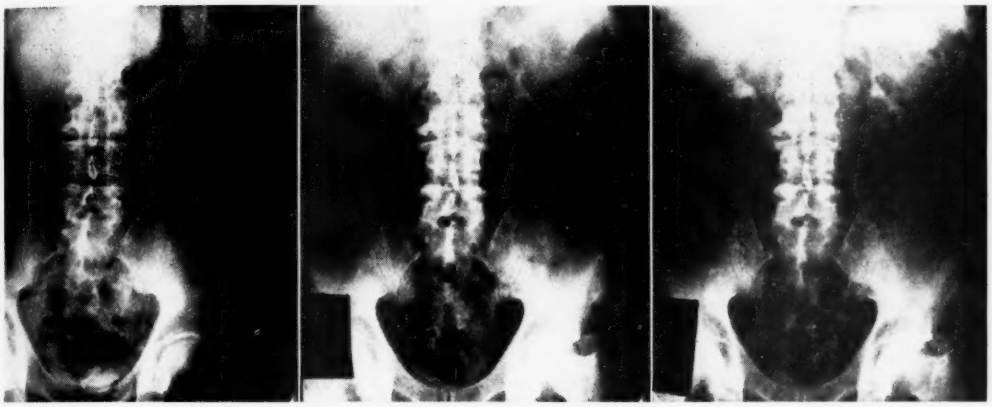

FIG. 7. Case 7. Intravenous pyelograms of patient with exacerbation of lymphatic leukemia. Blood urea nitrogen was 35 milligrams per cent at time pyelograms were made. Renal failure due to replacement of kidney by leukemic infiltrate 11 months later caused death.

16.5 grams, hematocrit 47 per cent, and white blood count 16,000 with a normal differential. Urinalysis revealed a specific gravity of 1.017, albumin (1+), no reducing substances, an occasional leucocyte, 8 to 10 erythrocytes, and 0 to 2 granular and hyalin casts per high-power field. Blood urea nitrogen was 18 milligrams per cent. Phenolsulfonphthalein excretion was 21 per cent at 15 minutes, and 17 per cent at 30 minutes, a total of 38 per cent in 30 minutes. Concentration to dilution ability was 1.017/1.002. Urea clearance was 51 per cent of normal. As might be expected, the intravenous pyelogram (Fig. 5) resulting from the injection of 30 milliliters of miokon showed "good visualization, essentially normal IVP." A right renal biopsy performed 48 hours after intravenous pyelography was reported as showing "acute severe proliferative glomerulonephritis." A biopsy on the same side, performed 5 months later, was reported as showing "early chronic severe interstitial fibrosis."

This case report is presented to re-emphasize the occasional inability not only of the intravenous pyelogram but also of other tests of renal function to disclose the presence of severe generalized renal disease.

CASE 6. H. G., a 65 year old colored male, had been followed since 1943 when he first was seen with symptoms of dyspnea, cough, hemoptysis, and edema of the ankles. Diagnoses of cardiovascular lues with aortitis, central nervous system lues with optic atrophy, and hypertensive cardiovascular disease were made at that time.

Physical examination in 1943 revealed a blood pressure of 174/70, pulse 100 per minute, and respirations 20 per minute. The pupils responded to light but not to accommodation. Grade I hypertensive retinal changes were recorded by the initial examiner. On examination of the chest, a grade II aortic systolic murmur was noted. The remainder of the physical examination was essentially noncontributory.

Laboratory studies revealed a positive blood serology for which antiluetic therapy was given. Nevertheless, the serology continued to be positive. Urinalysis in 1943 revealed specific gravity of 1.015, albumin (1+), 2 to 3 leucocytes, 0 to 2 granular, and 0 to 2 hyalin casts per high-power field. Repeated urinalyses since that time have shown similar findings. Nonprotein nitrogen determinations have varied from 43.4 milligrams per cent in 1944 to 67 milligrams per cent in 1957. The blood urea nitrogen was 17 milligrams per cent in 1944, and 43 milligrams per cent in 1956. In 1957 and 1958, values of 52 and 53 milligrams per cent were recorded. Serum creatinine was 3.3 in 1954, and 3 milligrams per cent in 1956. Urea clearance was 36 per cent of normal in 1956. Creatinine clearance was 45 per cent of normal the same year. Urea clearance in July 1958 was 24 per cent of normal. In 1954, the phenolsulfonphthalein excretion test showed 6 per cent of the dye excreted in 15 minutes and 30 per cent in 2 hours with good urine volumes each time. In 1956, the 15 minute phenolsulfonphthalein excretion was 5 per cent in 15 minutes, 16 per cent at 1 hour, and 9 per cent at 2 hours. In July of 1958, the phenolsulfonphthalein excretion was 2.5 milligrams per cent in 15 minutes, 10 per cent at 1 hour, and 7.5 per cent at 2 hours, this with a known residual less than 30 cubic centimeters. The concentration test performed in 1956 showed a maximum specific gravity of 1.018 with the morning specimen being 1.015. In July of 1958, the specific gravity of the morning specimen was 1.016, that of the first laboratory specimen 1.017; after an intake of 1,500 milliliters of water, the first hour specimen showed a specific gravity of 1.012.

An intravenous pyelogram (Fig. 6) was performed in July of 1958 using 50 per cent hypaque®.[2] This showed prompt bilateral visualization. The left caly-

[2] A brand of diatrizoate sodium.

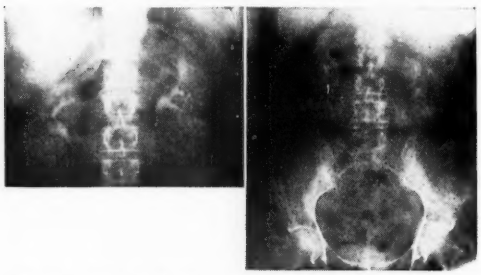

FIG. 8. Case 8. Pyelograms of patient with moderate impairment of renal function of unknown etiology taken at 10 and 20 minute intervals show negative findings.

ceal system was not well delineated, but there was no essential change from the previous examination in January of 1957. Impression of the roentgenologist was that this was an "essentially normal excretory urogram."

CASE 7. C. T., a 64 year old white male with lymphatic leukemia, was admitted to the hospital with complaints of persistent nausea and weakness accompanied by occasional vomiting and a diminished urinary output for a period of 6 weeks. A diagnosis of lymphatic leukemia had been made 1 year prior to this admission by a sternal marrow biopsy. Triethylene melamine, nitrogen mustard, and cortisone were given with excellent remission. Cortisone was continued at a 25 milligram daily level.

Physical examination at the time of admission revealed a blood pressure of 150/70, pulse rate of 80 per minute, and respirations of 20 per minute. Several 1 to 3 centimeter nodes were palpated in both inguinal regions and the axilla. The spleen and liver were both palpable. There was slight bilateral edema of the ankles. No other significant physical findings were noted.

Laboratory studies revealed a hemoglobin of 7 grams, hematocrit 22 per cent, white blood count 468,000 with 97 per cent lymphocytes. Findings by electrocardiogram were negative. Urinalysis revealed a specific gravity of 1.015, a trace of albumin, and 3 to 5 leucocytes per high power field. The blood urea nitrogen was reported as 28, 35, and 26 milligrams per cent during hospitalization. At the time the intravenous pyelogram (Fig. 7) was performed by intravenous injection of hypaque, it was reported as 35 milligrams per cent. There was prompt bilateral excretion of contrast medium with normal-appearing pelves and calyces. Repeat blood urea nitrogen determinations 4 months after the intravenous pyelogram disclosed a value of 26.5 milligrams per cent. Anuria 11 months after this admission caused death. Just prior to death blood urea nitrogen was 163 milligrams per cent. Cause of death at postmortem examination was recorded as uremia secondary to massive leukemic infiltration of both kidneys.

CASE 8. A. B., a 72 year old female, when first seen complained of bilateral edema of the ankles of 1 week's duration, although they had been "puffy" after a day's activity for many months. The patient had no dyspnea, orthopnea, or chest pain. For 3 to 4 months prior to the initial clinic visit she had noted 3 to 4 time nocturia.

Physical examination revealed a blood pressure of 180/100. A grade I systolic murmur, loudest at the apex and aortic area, was heard on examination of the chest. A 2 or 3 plus pitting edema was noted bilaterally. No other significant abnormalities were noted on physical examination.

Laboratory studies revealed the blood to be normal. Urinalysis showed a specific gravity of 1.019, a trace of albumin, 6 to 10 leucocytes and a few hyalin and a few granular casts per high-power field. The concentration to dilution test revealed a maximum concentration of 1.013, less than that recorded on a routine urinalysis, and dilution to 1.004. Phenolsulfonphthalein excretion was 9.3 per cent in 15 minutes, 28 per cent in 1 hour, and 1 per cent in 2 hours, or a total of 38 per cent excretion in 2 hours. The urea clearance was 38 per cent of normal. Blood urea nitrogen determinations before and after intravenous pyelographic study performed with 50 per cent hyapaque were 29 milligrams per cent. The diodrast renogram showed bilateral abnormal vascular and secretion phases. Despite this unequivocal evidence of impaired renal function, the intravenous pyelogram disclosed prompt bilateral visualization of normal-appearing renal pelves and calyces (Fig. 8).

DISCUSSION

The cases presented demonstrate the occasional failure of the intravenous pyelogram, at least as presently performed, to reflect the status of renal function accurately. The good early concentration of contrast medium during pyelography was seen in kidneys with moderate to marked evidence of bilateral impairment of renal function as determined by other tests. Although the degree of functional impairment was not always sufficient to suggest that one of the kidneys of the patients whose case histories were presented would be functionally inadequate to support life alone, certainly in every one of these instances serious consideration should be given to this possibility if nephrectomy were contemplated. The degree of functional impairment evident in Cases 1 and 6 would seem to eliminate serious consideration of nephrectomy. The normal pyelogram in the presence of an acute glomerulonephritis (Case 5), serves to emphasize that serious renal disease is not always associated with severe functional impairment or anatomic abnormality.

This evidence is not presented to attempt to discredit the role of intravenous pyelography in the evaluation of renal function. Until the advent of the diodrast renogram, it served as the only means of judging the functional status of

each kidney without instrumentation. However, these cases do re-emphasize the fact that sufficient early excretion of contrast medium to create a density comparable to or exceeding that of the twelfth rib and equaling that seen by retrograde pyelography can be achieved by 1 or each of 2 functionally impaired kidneys in the absence of striking anatomic abnormality. In the light of these observations we believe that the use of pyelographic evidence of normal function as a sole criterion for assuming that a kidney is capable of maintaining life after the removal of its mate seems unwarranted in the adult patient who is a candidate for elective nephrectomy. The implicit faith that we have, at times, seen placed in the intravenous pyelogram as a reflection of renal functional status is frightening. Of all tests of renal function, intravenous pyelography performed as it now is, with many different contrast media, available in different concentrations and using the density of a roentgenographic film as an indicator of functional capacity, seems to be the least quantitative. The factors which influence the radiographic end result after intravenous injection of one of the organic iodides used to visualize the renal collecting system are multiple. They include not only the roentgenologic technique but also the type and dosage of contrast medium used, injection time, the degree of hydration, the type of bowel preparation of the patient, and factors influencing renal blood flow.

The observations presented suggest that, in the adult, multiple tests of renal function are indicated prior to the elective removal of a kidney. In addition to a carefully performed urinalysis and intravenous pyelogram, it seems advisable to employ at least 1 test of total renal function such as the blood urea nitrogen level, phenolsulfonphthalein excretion, urea clearance, or concentration to dilution test and at least 1 other test of individual renal function, such as the differential phenolsulfonphthalein excretion, the differential indigo carmine excretion, or perhaps the diodrast renogram. Admittedly, the intravenous pyelogram will continue to play an important role in the evaluation of individual renal function. Under some circumstances, such as in the infant or in the emergency evaluation required in the seriously traumatized patient, practical consideration will often necessitate continued reliance on the pyelogram to reflect the functional status of each kidney. Whenever possible, however, this general information should be supplemented by other tests. Furthermore, as new contrast media are introduced, one should accept their ability to reflect functional status with increasing caution since the selection of a medium by the manufacturer seems to be based primarily on the degree of contrast it will produce and not on its ability to reflect the kidney's functional capacity.

SUMMARY

The renal functional status of patients having had intravenous pyelograms performed recently was reviewed. As expected, no difficulty was encountered in noting several instances in which an essentially normal intravenous pyelogram was associated with the presence of renal functional impairment. The degree of functional impairment was variable, but in some instances it was marked. Representative cases were selected for presentation. These observations support the wisdom of more complete evaluation of the functional status of kidneys which appeared to be normal by intravenous pyelography prior to elective ablative surgery.

EARLY POSTOPERATIVE ORAL FEEDING

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UNTIL FAIRLY RECENTLY too little attention has been paid to the effects of surgical trauma upon the patient and to the patient's response to surgery. As knowledge in this field increases, concepts change, and often long-accepted practices are modified and frequently discarded. It was in this manner that the principle of routine postoperative bed rest was rejected and early ambulation adopted.

Is it not possible that prolonged postoperative rest of the gastrointestinal tract through the withholding of food is likewise undesirable and, if not actually harmful, at least unnecessary?

Walters, Ravdin (11) Mulholland, and others expressed a need for correction of nutritional deficiencies earlier in the postoperative period than was possible by the accepted methods of management after gastrectomy. They therefore recommended early feeding by nasogastric tubes passed through the gastroenterostomy stoma or temporary feeding by jejunostomy. The food intake was well tolerated and, in part, corrected the deficiencies. However, the tubes were uncomfortable, and the jejunostomy added to the morbidity and mortality, with the result that these procedures have been used only when absolutely necessary.

The initial investigations of Cuthbertson, confirmed by the more recent studies of Moore and Ball, have shown that, characteristically, surgical patients exhibit a phase of nitrogen catabolism in the immediate postoperative period during which increased amounts of protein, nitrogen, and potassium are excreted. During this period, extending generally from 2 to 5 days, a negative nitrogen balance may persist in spite of a large protein intake, and caloric deficits are made up by oxidation of body fat with resulting weight loss.

At present, there is considerable difference of opinion regarding the value of protein therapy during this period. Significant reduction in the degree of negative balance by intravenous feeding has been reported by several including Elman, Riegel, and Beal, while the studies of Moore and of Wilkinson and their co-workers indicate that the negative nitrogen balance in the immediate postoperative period is a physiologic phenomenon and not completely amenable to correction.

Work in this field was reviewed by Rhoades who also reported upon a series of 55 patients fed and studied for 5 days after operation. He concluded that after surgery, such as gastric resection, the catabolic effect could be overcome by the generous intake of protein and calories. Revers and Eikelenboom stated that the negative nitrogen balance seen postoperatively was due to the decreased intake and recommended better postoperative nourishment.

No difference in the utilization of oral protein or intravenous hydrolysate has been demonstrated. The clinical superiority of the oral route results from the fact that a patient taking protein orally is readily able to receive an adequate caloric intake. The normal adult requires a minimum of 20 grams of nitrogen daily and a minimum of 120 calories per gram of nitrogen. The latter figures cannot easily be approached except by the oral route.

Zollinger, Elman, and others believe that daily variations in weight are the best clinical evaluation of a patient's nutritional state. According to Lund and Levinson, weight losses of from 1 to 1½ pounds a day or more are common after major operations and will continue until adequate dietary intake is restored. The work of Elman substantiates this belief.

Crandon sums up the present day consensus by recommending vigorous measures in order to place the patient in positive nitrogen balance as soon as feasible. He also believes that oral feeding is, without question, both preferable and more effective than the parenteral routes, but that it should be temporarily restricted after gastric resection in deference to the security of the suture lines believed to be vulnerable to rupture from excessive gaseous or fluid pressure, or to gastroenterostomy stomal function which may be temporarily impaired by edema. More commonly, he believes, oral feeding is restricted because of ileus.

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Since these objections have not been found to be valid there is no reason to delay oral feeding after elective gastric resection. Earlier unrestricted oral feeding after gastrectomy was begun at this hospital in 1947 and soon included abdominal surgery in general. To date, there are over 350 consecutive patients who have been fed early in the postoperative period after gastrectomy. Results have been simple to compare with controls, for there are two divisions in the surgical service. The other service has followed the more generally accepted method of postoperative management. Our controls are comparable cases, operations having been performed during the same time period by the staff and house staff. The technique and the postoperative management of the patient have depended upon the surgeon's choice.

In this article are presented a series of 20 consecutive cases of gastrectomy for ulcer or cancer from 1947 to 1949, at which time this study began, along with a similar series from the second service to serve as controls, another series of 30 patients operated upon from 1949 to 1951, again with a control series, and a final single series of 100 patients operated upon in late 1957 and 1958. No controls for the latter group seemed necessary.

Initially, liquids were given cautiously within the first 24 to 48 hours postoperatively (Table I). In the 1947 to 1949 group, all patients received liquids for the first postoperative meal. In the 1949 to 1951 group, only 60 per cent received liquids, and all of these, on the first postoperative day. However, in these years, 20 per cent of the postgastrectomy patients received a general hospital diet on the first postoperative day. With the confidence gained through experience a regular diet is now given routinely to all gastrectomy patients on the first postoperative day. Liquids frequently led to nausea, distention, gas pains, and anorexia, none of which are encountered when regular meals are given.

In Table I a breakdown is given of the 3 study groups as to the percentage fed liquid and/or regular diets in the earlier postoperative period. All 100 patients in group III (1957 to 1958) were fed on the first postoperative day.

Almost all the patients are males with a white to Negro ratio of 2 to 1. In age, the patients ranged from 20 to 74 years, with an average age of 42 and a mean of 38 years. Ninety per cent were operated upon for peptic ulcer. Duodenal ulcers occurred 3 times as frequently as gastric ulcers. Of these, 40 per cent were operated upon because of hemorrhage, 40 per cent for intractable pain, and 7 per cent for pyloric obstruction. These operations were performed by various members of the staff and house staff. In our study groups, all gastrectomies were performed in the usual manner of Hofmeister, after it was ascertained that all gastric bleeders were ligated before the anastomosis was begun. Recently, early postoperative feeding has been employed in Billroth I anastomoses with the same good results.

TABLE I.—TYPE OF DIET AND POSTOPERATIVE DAY FIRST ADMINISTERED

	Postoperative day	*Diet*		*Average for regular diet, days*
		Liquid	*Regular*	
		per cent		
Group I				
(20 patients, 1947 to 1949)	1	65		
	2	20	45	2.7
	3	5	55	
Group II				
(30 patients, 1949 to 1951)	1	60	20	
	2	—	63	2.2
	3	—	17	
Group III				
(100 patients, 1957 to 1958)	1		100	1
	2			
	3			

TABLE II.—RELATIONSHIP OF EARLY FEEDING TO DISCONTINUANCE OF SUCTION

	Oral diet begun, postoperative day			*Day suction discontinued*
	Liquid	*Soft*	*Regular*	
Group I	1.2		2.7	2.5
Control	3.8	5.3	17.6	4.0
Group II	1.0		2.2	1.8
Control	2.7	4.2	7.6	3.5
Group III			1.0	1.0

The choice of anesthetic has been no problem. Continuous spinal, continuous epidural, and inhalation anesthesia has been used. The anesthetic agent, including ether, seems to have no appreciable effect on the patient's ability to tolerate a regular diet on the first postoperative day.

Early ambulation has been employed routinely. Constant suction is maintained with a Levin tube for 24 hours (Table II), and upon removal of the tube oral feeding of a regular diet is begun. Milk is the only item of food that is prohibited, for it seems to produce gas pains. Since the postoperative subtotal gastrectomy patient cannot eat too much at any one meal be-

TABLE III.—POSTOPERATIVE INFUSIONS

	Infusion, postoperative per patient, 1,000 c.c.
Group I (20 patients)	6.0
Control	15.0
Group II (30 patients)	4.7
Control	8.3
Group III (100 patients)	3.0

TABLE IV.—SERUM PROTEINS ALBUMIN-GLOBULIN RATIO COMPARISON

	Average serum proteins as A/G ratio		*Ten day postoperative weight loss, pounds*
	preoperative	*postoperative*	
Group I	4.0/2.6	3.6/2.5	2.6
Control	4.1/2.6	3.4/2.8	5.7
Group II	4.0/2.5	4.0/2.8	3.2
Control	3.9/2.4	3.7/2.4	7.6
Group III	4.2/2.2	4.3/2.4	1.4

TABLE V.—AMBULATION, SEDATION, AND DISCHARGE

	Ambulatory, postoperative day	*Sedation, postoperative days*	*Discharge, postoperative day*
Group I	2.7	3.3	13.0
Control	7.1	5.4	19.6
Group II	1.6	3.1	12.0
Control	2.7	5.0	16.3
Group III	1.0	2.9	10.2

cause of the reduction in the stomach's capacity, 6 daily feedings are given.

Table II shows a comparison of the two groups and the controls for the periods 1947 to 1949 and 1949 to 1951. Note in particular the shorter delay in feeding orally and the shorter period of gastric suction required in group III. As a consequence, there is a marked difference in the number of infusions necessary to maintain the two groups (Table III). In the cases under study, it is demonstrated that the earlier the patient is fed, the less parenteral fluid is required. At present, 1,000 cubic centimeters of dextrose in distilled water are given on the day of operation, and 1,000 cubic centimeters each of dextrose in water and saline the following day.

Table IV shows the serum protein determination and the weight loss postoperatively. We believe that the constantly lower figures of weight loss postoperatively in those patients who were fed early is of considerable significance. The range of weight loss in the two groups is comparable, but those who were fed early stabilized about the fourth postoperative day and began a progressive weight gain at that time, so that

TABLE VI.—POSTOPERATIVE DEATHS

	No.	
Group I	0	
Control	2	1 postoperative hemorrhage, 1 pancreatitis
Group II	0	
Control	3	1 strangulating obstruction, 1 wound dehiscence, 1 unknown
Group III	1	Peritonitis and adrenal necrosis

TABLE VII.—COMPLICATIONS ENCOUNTERED

	Group I	*Control*	*Group II*	*Control*	*Group III*
Distention	6	11	4	14	3
Nausea and vomiting					1
Wound dehiscence	1	2	1	2	1
Wound infection	1		1	3	
Pneumonia	1	2	1	1	
Atelectasis	1	2	1	1	
Postoperative hemorrhage		3		2	1
Postoperative obstruction (small bowel)					1
Cystitis			1		
Thrombophlebitis				1	
Pancreatitis		1			
Leakage from duodenal stump		1			1

by the tenth postoperative day there was an average weight loss of only 1.4 pounds.

One notable effect of early feeding and early ambulation has been the feeling of relief to the patient. The surgical ordeal is over, fear of producing former ulcer pains is abated, and the anticipation of being well is not restricted. Suggestion, here, works at its best in behalf of the patient.

The figures in Table V show that the sooner a patient can be fed the easier it is for him to ambulate. With earlier ambulation and earlier feeding, pain, distention, and apprehension are diminished, resulting in a marked decrease in the demand for narcotics. Likewise, these patients can be discharged much sooner because of their better physical and mental condition.

At present, narcotics are required for an average of 2.9 days postoperatively. Usually, codeine is sufficient after the second postoperative day. By the third or fourth day most patients walk to the canteen without assistance. All are ready for discharge before the tenth day, but, since many are from a considerable distance away and frequently return home by public conveyance, they have not been released before the tenth postoperative day.

Postoperative deaths were much lower in this series than in those patients fed in the more conventional manner (Table VI). In the group

of 150 cases reviewed, there was 1 young man who died on the fourteenth day after subtotal gastrectomy for pyloric obstruction of several months' duration. Autopsy indicated a generalized peritonitis and bilateral adrenal necrosis. He had been given large doses of cortisone since the fourth postoperative day, because of adrenal failure. The peritonitis was due to leakage from the duodenal stump. There was no evidence of rupture, just a complete lack of healing. At autopsy, a probe could be passed between the sutures into the lumen of the duodenum. He did not tolerate early feeding.

There have been far fewer other complications in patients who were fed early (Table VII). In fact, in recent years there have been even fewer since feeding has been started on the first postoperative day.

The case cited was the only instance in which there was leakage from a duodenal stump. In no instance did leakage occur at the gastroenterostomy suture line. In this series there were only 2 instances of postoperative hemorrhage. In 1 of these patients reoperation was required on the sixth postoperative day to control bleeding at the lesser curvature angle. On the first postoperative day feeding was again begun and the patient did well. The other instance of bleeding ceased spontaneously.

There has been less than 1 per cent failure in our efforts at early feeding. These were manifested by nausea and occasional vomiting and distention of a mild to moderate degree. These patients have not been problems and were controlled by aspiration of the stomach, usually only once, after which diet was tolerated. Stomal impairment due to edema, on or after the first postoperative day, was not demonstrated. One instance of acute gastric dilatation occurred on the fourth postoperative day. Most of the failures, we believe, were not due to the method but to failure in adequately preparing the patient preoperatively, from a psychologic standpoint, to get well rapidly.

SUMMARY AND CONCLUSIONS

The catabolic effect of surgery, such as gastric resection, needs to be corrected earlier in the postoperative period. This can best be accomplished by oral feeding.

After gastric resection, a general hospital diet may be fed the patient on the first postoperative day without fear of adverse effect. Early in the postoperative period, solids are tolerated better than liquids. Six small meals daily are required because of the small gastric reservoir.

The patient is happier and regains confidence much more quickly when eating is not restricted. Gas pains, nausea, and distention occur much less frequently, are lesser in degree, and the amount of sedation employed is greatly reduced. The need for infusions is likewise reduced.

The postoperative weight loss is held to a minimum, and the majority of patients are gaining weight by the time of discharge on the tenth postoperative day.

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THE SURGEON'S LIBRARY

Reviews of New Books

THE MONOGRAPH *Color Atlas and Management of Vascular Disease*,[1] was written by two eminent internists, and is intended to aid those dealing only occasionally with peripheral vascular disease. Most of the reproductions are in full color and are available as transparencies. These illustrations are of good quality and are well chosen for teaching purposes.

Unfortunately, this 170 page book does not present all subjects on peripheral vascular disease in a uniform style. For example, acute arterial occlusion is discussed rather fully under such subheadings as diagnostic signs, physiologic changes, adaptive mechanisms, and treatment. On the other hand, Buerger's disease is given in the presentation of four illustrated case histories without any general discussion whatsoever.

Because the authors are internists, the management of the various syndromes is discussed primarily from the medical viewpoint. Surgical measures are only mentioned in passing.

Students, house officers, and internists should find this atlas a useful aid in the recognition of peripheral vascular lesions. —*Harold Laufman.*

THE RESULTS of thorough investigation of the diagnostic possibilities of artificially induced pneumoperitoneum in a large number of patients is presented in the monograph entitled *Das diagnostische Pneumoperitoneum*.[2] Usually, pneumoperitoneum was induced as a preliminary measure for laparoscopy. For many of the 1,120 patients with whom the report is concerned, the diagnosis could be established by x-ray examinations of the abdominal organs made roentgenologically visible by pneumoperitoneum. Thus, laparoscopy seemed often to be only a further diagnostic measure.

Oxygen was preferred to various other gases for pneumoperitoneum because it is absorbed in considerably less time than other gases. The amount of gas used for filling the abdomen varied from 2.5 to 3.5 liters. Fluoroscopy was employed prior to making the roentgenogram in order to establish the optimal position of the patient for visualization of the different organs.

The indications for pneumoperitoneum varied considerably. Among them were adhesions, enlargement of the liver and the spleen, renal, adrenal and pancreatic tumors, diaphragmatic disturbances, diseases of the abdominal wall, abscesses of the psoas region, tumors of the mesentery, and diseases of the female pelvic organs. Definite contraindications mentioned are "the acute abdomen" and subphrenic abscess. A rather long list of possible complications of pneumoperitoneum were mentioned. From these, it seems that pneumoperitoneum should be used only when other diagnostic methods fail to reveal the source of the pathologic abdominal or retroperitoneal process.

The monograph includes a large number of well chosen roentgenograms that act as a guide for the physician interested in the method. This monograph is recommended to everyone who uses laparoscopy or pneumoperitoneum as a diagnostic aid in clinical medicine but for others it definitely would be of academic interest only. —*Herbert A. Roedling.*

THE DELIGHTFUL BOOK *The Surgeon and the Child*[3] contains 247 pages of informal chatting with one of the country's best known pediatric surgeons about a field in which he is so secure that he can safely and with tongue-in-cheek abstain from pretenses. Although ostensibly aimed at the undergraduate student, surgical and pediatric house officer, and general practitioner, it is also packed with simple, yet important, suggestions which should be of practical importance to the experienced general surgeon.

With no pretenses at having written just another textbook in pediatric surgery, the author can cast off the cloak of omnipotence and comprehensiveness and so pick and choose subjects for emphasis that he thinks important. One chapter begins as follows: "So many articles recently have been written on the diagnosis of interatrial septal defects that any detailed review by me would be repetition—more honestly plagiarism." This humble philosophy so seldom practiced yet so sorely needed in medical literature is then characteristically followed by a succinct, pithy, and solid discussion of the subject.

The book's outstanding characteristic is the underlying philosophy and humanistic approach of its

[1]COLOR ATLAS AND MANAGEMENT OF VASCULAR DISEASE. By William T. Foley, M.D., F.A.C.P., and Irving S. Wright, M.D., F.A.C.P. 170 pages, illustrated. $18.00. New York: Appleton-Century-Crofts, Inc., 1959.

[2]DAS DIAGNOSTISCHE PNEUMOPERITONEUM. By Prof. Dr. Med. A. Gebauer. Preface by Prof. Dr. F. Hoff. 69 pages, 78 illustrations. $4.30. Stuttgart: Georg Thieme Verlag, 1959.

[3]THE SURGEON AND THE CHILD. By Willis J. Potts, M.D. 255 pages, illustrated. $7.50. Philadelphia and London: W. B. Saunders Co., 1959.

author who sets the tone of the work with a chapter on "The Heart of a Child"—a section devoted not to discussions of myocardial difficulties but to the emotional and philosophic aspects of the child as he reacts to the surgical environment.

Despite its relaxed and informal tone, the book is filled with simple, practical, and important ideas for the physician. Not only do we learn that the pleural of ductus is still ductus—"fourth declension" but the author in a bold manner states simply and didactically how to repair it. No nonsense with the pros and cons of what may or may not be the approach, but merely a statement of how one goes about it. The didactic thunder of some of the statements is so obviously perpetrated for purposes of emphasis that no offense can be taken and it indeed adds charm.

It is refreshing to have a verdant book of this nature appear among the dry leaves of most current surgical texts. Physicians of essentially any specialty interest will find that Pott's book is both interesting reading and of valuable help in the care of a child requiring surgery. —*Ben Eiseman.*

THE AUTHOR of *Die Wirbelsaeulenleiden und ihre Differentialdiagnose*[4] has been interested in the diseases of the spine for more than 25 years.

This monograph is a revised edition of the author's previous monograph of the same title published in 1953. Included in the second edition is a discussion of the conservative and surgical treatment of tuberculosis of the vertebral column. The new edition is broadened to include other diseases of the vertebral column and their differential diagnosis.

There is a chapter on infectious diseases of the spinal column which includes osteomyelitis due to staphylococcus and streptococcus. Osteomyelitis due to septic foci secondary to bacillus, typhus, and other causes such as erysipelas and pneumonia are described. Vertebral lesions due to nonbacterial diseases such as actinomycosis, blastomycosis, and syphilis are described.

Spondylitis ankylopoietica and Scheuermann's disease receive serious consideration since they are clinically and socially important. Vertebra plana of several types are described. Many forms of congenital anomalies are described and illustrated with roentgenograms. There is a chapter on degenerative arthritis, describing the condition for each region of the spinal column. Osteoporosis and osteomalacia, as well as tumors of the spine, both secondary and primary, are well illustrated and discussed. Diseases of the sacrum and the sacroiliac joint receive special attention.

The final chapter acts as a guide for the differential diagnosis of the diseases of the vertebral column. The author illustrates the various diseases of the spine with excellent roentgenograms. As far as possible he bases his discussion on the etiology and the pathogenesis of the disease.

This book is more than an atlas of roentgenograms of the spinal column. It includes the differential diagnosis, a summary of the pathogenesis, and the treatment of the various diseases affecting the spine. It contains an extensive bibliography of the modern literature on this subject. It is so designed that it makes an excellent reference book to aid the clinician in a difficult or doubtful case of disease of the spine.

—*Emil D. W. Hauser.*

[4]DIE WIRBELSAEULENLEIDEN UND IHRE DIFFERENTIALDIAGNOSE. By Prof. Dr. J. E. W. Brocher, 457 pages, 287 illustrations. DM 128.—Stuttgart: Georg Thieme, 1959.

THE TWENTY-SEVENTH EDITION of *Gray's Anatomy of the Human Body*[5] is the American centennial edition. A few words will suffice to recommend a book as well known as this.

Like the previous editions, the new version is occupied primarily with systematic anatomy; the same general plan and order of the book continue. The brief summaries of embryology and histology have been retained, in many cases improved, and are presented in more consistent form throughout.

One of the most extensive changes concerns the chapter on the central nervous system. This section has been reorganized and rewritten, permitting a significant reduction in the amount of space allotted to it. Other chapters have been rewritten or reorganized to a lesser degree.

Most of the terminology is based upon the *nomina anatomica.* In the majority of cases, the text employs the English translation with the official Latin term, and occasionally some alternative terms, in parentheses. In other places the Latin is used directly in the text.

Gray's *Anatomy of the Human Body* continues to be one of the finest books in its field. Everyone concerned with this centennial edition can be proud of it.

—*Carolyn E. Thomas.*

IN AN IMPRESSIVE MONOGRAPH entitled *Les lésions traumatiques de l'uretère*[6] the well known French urologists, Cibert and Revol, deal with the subject of traumatic lesions of the ureter. The often extremely difficult and distressing problems of ureteral repair or replacement after surgical injury of the ureter are carefully studied, with the accent on injuries during gynecologic pelvic procedures. If the lesion is detected at such time, immediate repair is usually easier and more rewarding than if the lesion is detected at a later date; all the different possibilities of repair or transplant are mentioned, their merit studied, depending on the type of lesion and under varying circumstances, and a procedure suggested that in each case would seem to give the best functional and anatomic result. The authors, experienced in ileal loop transplants of both bladder and ureter, study this question critically and extensively. Different techniques are reviewed and their own experiences compared with those of others. The actual question of splinting and temporary urinary diversion is mentioned but incompletely answered. Because separate chapters are devoted to the same type of lesions caused by obstetric and urologic operations, appendectomy, hernia repair, and operations on colon and rectum, the authors have repeated themselves on several occasions. The world literature is

[5]ANATOMY OF THE HUMAN BODY. By Henry Gray, F.R.S. Edited by Charles Mayo Goss, M.D. 27th ed. 1458 pages, 1174 illustrations. $17.50. Philadelphia: Lea & Febiger, 1959.

[6]LES LESIONS TRAUMATIQUES DE L'URETÈRE. By Jean Cibert and Michel Revol. 281 pages, illustrated. 4,200 fr. Paris: Masson et Cie, 1959.

extensively and critically reviewed with a carefully chosen bibliography at the end of each chapter.

This book contains a thorough and complete outline on the treatment of ureteral injury. There is a small section on accidental blunt and sharp abdominal traumatism as the cause of ureteral injury with details on diagnosis and treatment.

—*H. W. Ten Cate.*

VOLUME II of *A Text on Systemic Pathology*,[7] edited by Otto Saphir and compiled with the assistance of 8 contributors, brings to almost 2,000 fact-filled pages the achievement of the senior author's goal "—a forthright text." This volume, illustrated with 978 plates, includes 13 subdivisions: The alimentary tract and peritoneum; the oral cavity, pharynx, nasopharynx, branchial apparatus, and salivary glands; the teeth; the nose and paranasal sinuses; the ear; the eye and ocular adnexa; the liver, gallbladder, and bile ducts; the pancreas; the endocrine glands; the skin; the organs of locomotion; the brain, meninges, and spinal cord; the peripheral nerves.

Chapters 2, 3, 4, and 5 cover the regions of the body which are rarely more than touched upon in older textbooks of pathology. In these, as in other chapters, important anatomic and embryologic data are supplied as they relate to an understanding of the pathologic processes which follow in the text. Refreshing pauses are inserted as the authors spell out the Latin and Greek stems of otherwise meaningless words while line-length bibliographic sketches are helpfully placed to soften the "odium of the eponym" (Cushing's Disease: H. W. Cushing, American Surgeon 1869–1939).

Bibliographic references are thorough, and the index is complete and altogether usable.

It would seem that the amount of factual material in this, as in Volume I, might overwhelm the medical student or at least discourage him from specializing in pathology. On the other hand, to the busy practicing pathologist, the two companion volumes assume the essential aspects of a quick reference library. Were any criticisms justified they would be to the effect that the rare and the commonplace have alike been documented in the same bold print. In the final analysis, however, "fine print" may well be overlooked when bookshelf documents are being hastily consulted in search of help in problem cases.

—*Malcolm B. Dockerty.*

THE PUBLICATION of the book *Pancreatitis*[8] which is encyclopedic in character is timely because of the widespread interest in the subject. A thorough review of the literature on pancreatitis is supplemented by an excellent bibliography. The presentation of the material is logical in that the chapters on the clinical manifestations of the disease and on treatment follow the sections on etiology, physiology, and pathology.

Data on 163 autopsies are presented in which various degrees of pancreatitis were found. However, in only 17 cases was the pancreatitis considered the primary cause of death. It would appear, therefore, that many of the inflammatory changes noted in the pancreas at autopsy were the result of nutritional and agonal changes accompanying other diseases. This conclusion is supported by the fact that only 13.5 per cent of the cases were classified as recurrent pancreatitis which is amenable to effective treatment by operation.

The sections on anatomy and physiology show many lapses. The quoted incidence of visualization of the pancreatic duct during cholangiography is 7 to 47 per cent. The authors fail to mention the published figure of a 61 per cent incidence of reflux at operative cholangiography. Contraction of the gallbladder does not "add a pressure of 25 cm. to a normal pressure of 30 cm. in the common bile duct." In fact, under such conditions the gallbladder could not possibly contract; and certainly the normal pressure in the common bile duct is not 30 centimeters, but usually less than 15 centimeters. In quoting Flexner's work on experimental pancreatitis, the essential point that concentrated bile is necessary to produce pancreatitis is completely missed. Consequently, the authors fail to point out that the absence of inflammation, in experiments in which pancreatic juice is caused to course through the gallbladder or bile through the pancreatic duct, should not be an unexpected finding.

Calculations on protein loss in pancreatic secretion cannot be correct if based upon the quoted figure of 700 cubic centimeters as the 24 hour output of the human pancreas. Actually, this organ secretes 1,500 to 4,000 cubic centimeters of juice daily. Acid does not activate trypsinogen, nor does calcium. There is no firm evidence that elastase and collagenase are present in the pancreas of human beings, and the extensive discussion of the action of these hypothetical enzymes on the blood vessels of the human pancreas does not seem warranted. Acetyl-l-tyrosine ethyl ester, which is mentioned as a possible substitute for elastase, actually is a specific substrate for chymotrypsin.

The section on pathology, as would be expected, is excellent, but no mention is made of pancreatography which during the past 10 years has yielded new and important information on the pathologic process in pancreatitis and its complications in the living.

In the chapter on the treatment of severe pain during an attack of acute pancreatitis, every analgesic and nerve blocking drug or procedure is discussed, but no emphasis is placed on the use of nasogastric suction as the physiologic method for controlling pain, by putting the gastrointestinal tract at rest. With effective suction, only 2 or 3 small doses of demerol hydrochloride will control pain in the most severe case.

The treatment of fat intolerance, which is the most common complication of pancreatitis, is presented in a cursory fashion. A bland diet which does not exclude whole milk, eggs, cream, and butter is ineffective, and the recommendation of cream soups and skim milk is not only anomalous but is an indication that the

[7] A TEXT ON SYSTEMIC PATHOLOGY. Edited by Otto Saphir, M.D. Vol. II. 1083 pages, illustrated. $38.00. New York and London: Grune & Stratton, 1959.

[8] PANCREATITIS; A CLINICAL-PATHOLOGIC CORRELATION. By Herman T. Blumenthal, Ph.D., M.D., and J. G. Probstein, M.D. Foreword by R. M. Zollinger, M.D. 379 pages, 58 illustrations. $9.50. Springfield, Ill.: Charles C Thomas, 1959.

problem is not understood. There is no discussion of the evidence that after sphincterotomy, the pancreas will regenerate if a proper fat free diet is maintained postoperatively.

Advocacy of cystogastrostomy as the treatment of pseudocysts would not be supported by most surgeons today, even if the cyst were in a retrogastric position. No mention is made of sphincterotomy as being effective in the treatment of pseudocysts, although this subject has been discussed in the literature for the last 6 years.

The main weakness of this book is not due to these relatively minor criticisms but to the fact that the authors have attempted to do too much. The subject is so large and so diverse that it is one thing to compile a source book and quite another to evaluate critically a subject in which so many disciplines are involved. The state of confusion which plagues the subject of pancreatitis is not resolved in this book. This problem will be solved eventually, not by examination of autopsy material but by properly controlled observations on the living individual who is suffering from pancreatitis. —*Henry Doubilet.*

THE BOOK entitled *Trauma*[9] by Harrison L. McLaughlin and 21 collaborating authors is an excellent summary of the subject. The associate authors are for the most part faculty members of the College of Physicians and Surgeons, Columbia University.

The book is divided into five major sections. The first section considers the general effects of trauma, the principles of treatment, and thermal and vascular injuries. This portion of the book is excellent and is of particular value to students, interns, and residents of surgical specialties. The second and third divisions of the book cover injuries to the upper and lower extremities. The fourth section deals with injuries of the trunk, including the pelvis, abdomen, chest, vertebral column, cervical spinal cord, and the low back. The fifth division concerns trauma to the head and special senses, including the skull and brain, the auditory and nasopharyngeal structures, the maxillofacial area, and the eye.

It is difficult to correlate all of the various aspects of injury in one volume; however, the authors have performed their task well. The book emphasizes the importance of the "physician-team approach" to diagnosis and treatment of the seriously injured patient.

The logic of diagnosis and treatment is enhanced by a brief review of functional anatomy of the region under discussion in each chapter. Illustrations are excellent and pertinent.

The book is valuable as a quick reference for the physician concerned with trauma and as a text for the student, intern, and surgical resident.

—*William A. Larmon.*

THE RECENT STUDY of Raymond Denis entitled *Adénomectomie endo-urétrale de l'adénome prostatique et traitement du cancer de la prostate* should be considered an important contribution to European literature on this subject.[10] Covering the entire field of endoscopic resection for different indications, the book deals separately with partial and total transurethral adenomectomy for benign prostatic hyperplasia. In the introduction, the author states that this study was written for those urologists who are not completely satisfied with the results of open procedures and have become interested again in the transurethral approach. The book gives, however, more than a "brush-up" and is a solid outline for resident and beginner. Many drawings illustrate the techniques and their complications.

The author believes that for a complete resection the surgeon must provide rectal support during the procedure instead of leaving this to an assistant. He claims, therefore, that an instrument which can be used with one hand only is indispensable. Results in 10 per cent of the partial resections performed between 1934 and 1947 by the author were satisfactory. Prolonged hematuria and pyuria, resulting in recurrent obstructive symptoms, developed in 5 per cent of the patients. He states that recurrent symptoms are never due to recurrent tissue but to remaining tissue only; therefore, the objective of endoscopic resection for benign prostatic hyperplasia should always be complete adenomectomy.

This monograph does not present any new methods or techniques for the American urologist. Written in clearly understandable French, it provides a rich source of information for the young European urologist. The world literature is largely covered, but many names in the bibliography are misspelled.

—*H. W. Ten Cate.*

THE MODERN AND COMPREHENSIVE TREATISE *Radiation Therapy*[11] represents a commendable blend of scholarship and extensive clinical experience. An initial chapter deals with physical and biologic factors affecting radiation response. The subject of dosimetry is detailed in explicit and understandable terms. The bulk of the subject material is subdivided along anatomic lines. The epidemiologic, etiologic, and pathologic features of the neoplasms which characterize each anatomic region are dealt with briefly but authoritatively. Major emphasis in each chapter is reserved for the details of treatment. The temptation to overstate the case of radiotherapy has been avoided. Indications and contraindications for the selection of each of the major modalities of treatment are very carefully set forth. When radiation therapy is to be employed, practical details of treatment are given. One point in technique which is repeatedly emphasized is the progressive reduction in field size with increasing dose and with concentric regression of treated lesions. This is an important consideration in minimizing complications after radiation, and this has been stressed more explicitly in the book than in any other on radiation therapy of which the reviewer is aware. Although the advantages of supervoltage equipment in the practical management of a variety

[9]TRAUMA. By Harrison L. McLaughlin, M.D. 784 pages, illustrated. $18.00. Philadelphia and London: W. B. Saunders Co., 1959.

[10]ADÉNOMECTOMIE ENDO-URÉTRALE DE L'ADÉNOME PROSTATIQUE ET TRAITEMENT DU CANCER DE LA PROSTATE. By Raymond Denis. 194 pages, 100 illustrations. 2.500 fr. Paris: Masson et Cie, 1959.

[11]RADIATION THERAPY. By Walter T. Murphy, M.D. 1041 pages, illustrated. $25.00. Philadelphia and London: W. B. Saunders Co., 1959.

of deep seated neoplasms are clearly stated, space is also devoted to the techniques of orthovoltage equipment, such as is widely available to radiologists in general. The illustrations are excellent, and it will, no doubt, be educational for readers unfamiliar with radiotherapy to see so many photographs of patients apparently cured by radiotherapy alone, since it is a widespread misconception that radiotherapy is useful primarily for palliation in cases that are considered hopeless.

Current trends in the experimental laboratory having to do with the modification of radiation sensitivity through the use of oxygen and chemical potentiating agents are touched upon only briefly. However, a commendable effort has been made to include the voluminous literature in these fields; many references to papers as recent as 1958 attest to the author's effort to make the book as up-to-date as possible. Extensive bibliographies are given at the end of each chapter, and these seem to have been carefully chosen to reflect some of the varying viewpoints regarding treatment of specific types of neoplasms.

In summary, this is an excellent, comprehensive, much-needed new textbook on radiation therapy. The author's clinical experience has been very happily coupled with clarity of literary style, a logical format, excellent illustrations, and scholarly bibliographies. This book will be valued as a reference source by all who deal with the treatment of malignant neoplasms.

—*Henry S. Kaplan.*

BOOKS RECEIVED

Books received are acknowledged in this department, and such acknowledgment must be regarded as a sufficient return for the courtesy of the sender. Selections will be made for review in the interests of our readers and as space permits.

INTRODUCTION TO COLPOSCOPY; A DIAGNOSTIC AID IN BENIGN AND PRECLINICAL CANCEROUS LESIONS OF THE CERVIX UTERI. By Karl A. Bolten, M.D., and William E. Jaques, M.D. 76 pages, 53 illustrations. $7.75. New York and London: Grune & Stratton, 1960.

A PRACTICAL GUIDE FOR GENERAL SURGICAL MANAGEMENT. By Julian A. Sterling, M.D. 67 pages. $3.00. New York, Washington, Hollywood: Vantage Press, 1960.

A MEDICAL SOURCEBOOK; A REFERENCE HANDBOOK FOR LEGAL, LEGISLATIVE AND ADMINISTRATIVE PERSONNEL. By Fred A. Mettler, M.D. 1000 pages, illustrated. $25.00. Boston and Toronto: Little, Brown & Co., 1959.

PRATIQUE OBSTETRICALE. By M. Lacomme. Vol. I—pp. 1-868 and Vol. II—pp. 871–1719. Illustrated. 23.000 fr. Paris: Masson et Cie, 1960.

MONOGRAPHIES CHIRURGICALES (collection Henri Mondor). CHIRURGIE DU RACHIS. By Andre Sicard. 478 pages, illustrated. 7.000 fr. Paris: Masson et Cie, 1959.

GYNECOLOGICAL THERAPY. By Josef Novak, M.D. 258 pages, illustrated. $8.50. New York, Toronto, and London: McGraw-Hill Book Co., Inc., The Blakiston Division, 1960.

HANDBOOK OF PHYSIOLOGY; A CRITICAL, COMPREHENSIVE PRESENTATION OF PHYSIOLOGICAL KNOWLEDGE AND CONCEPTS. Section 1: Neurophysiology. Vol. II. Editor-in-Chief: John Field. Section Editor: H. W. Magoun. Executive Editor: Victor E. Hall. Washington, D. C.: American Physiological Society, 1960. Baltimore: The Williams & Wilkins Co., exclusive U. S. agents.

THE HUMAN SPINE IN HEALTH AND DISEASE; ANATOMICO-PATHOLOGIC STUDIES. By Georg Schmorl (†1932), M.D. Clinicoradiologic Aspects by Herbert Junghanns, M.D. The first American edition, translated and edited by Stefan P. Wilk, M.D., and Lowell S. Goin, M.D. 285 pages, 419 illustrations. $21.00. New York and London: Grune & Stratton, 1959.

ANATOMY REGIONAL AND APPLIED. By R. J. Last, M.B., F.R.C.S. 2nd ed. 741 pages, 372 illustrations. $15.00. Boston: Little, Brown & Co., 1959.

STRAHLENBIOLOGIE, STRAHLENTHERAPIE, NUKLEARMEDIZIN UND KREBSFORSCHUNG; ERGEBNISSE 1952–1958. Edited by H. R. Schinz, H. Holthusen, H. Langendorff, B. Rajewsky, and G. Schubert. Assisted by numerous specialists. 998 pages, illustrated. $65.50. Stuttgart: Georg Thieme, 1959.

HERITABLE DISORDERS OF CONNECTIVE TISSUE. Victor A. McKusick, M.D. 2nd ed. 333 pages, illustrated. $12.00. St. Louis: The C. V. Mosby Co., 1960.

LEUKOCYTE ANTIGENS AND ANTIBODIES. By Roy L. Walford, M.D. 182 pages, illustrated. $6.75. New York and London: Grune & Stratton, 1960.

THE SURGERY OF THEODORIC CA. A.D. 1257. Translated from the Latin by Eldridge Campbell, M.D., and James Colton, M.A. Vol. II (Books 3 and 4). 233 pages. New York: Appleton-Century-Crofts, Inc., 1960.

SURGICAL PHILOSOPHY IN MASS CASUALTY MANAGEMENT; WITH DETAILED NOTES ON PRACTICAL CARE. By Warner F. Bowers, M.D., and Carl W. Hughes, M.D. 204 pages. $6.75. Springfield, Ill.: Charles C Thomas, 1960.

MITRA OPERATION FOR CANCER OF THE CERVIX; EXTRAPERITONEAL PELVIC LYMPHADENECTOMY AND RADICAL VAGINAL HYSTERECTOMY. By Subodh Mitra, M.B., F.R.C.S. (Edin.). Foreword by Prof. Dr. Robert Schroeder. 93 pages, 38 illustrations. $6.00. Springfield, Ill.: Charles C Thomas, 1960.

ELECTROHYSTEROGRAPHY; THE ELECTRICAL ACTIVITY OF THE HUMAN UTERUS IN PREGNANCY AND LABOR. By Saul David Larks, B.S.E.E., M.S. (E.E.), Ph.D. 123 pages, illustrated. $5.75. Springfield, Ill.: Charles C Thomas, 1960.

INTUSSUSCEPTION IN INFANTS AND CHILDREN. By Mark M. Ravitch, M.D. 121 pages, illustrated. $9.00. Springfield, Ill.: Charles C Thomas, 1959.

A PRACTICE OF ANAESTHESIA. By W. D. Wylie, M.B. (Cantab.), M.R.C.P., F.F.A.R.C.S., and H. C. Churchill-Davidson, M.D.(Cantab.), F.F.A.R.C.S. 1056 pages, 246 illustrations. $20.00. Chicago: The Year Book Publishers, Inc., 1960.

CANCER AND ALLIED DISEASES OF INFANCY AND CHILDHOOD. Edited by Irving M. Ariel, M.D., and George T. Pack, M.D. 27 contributing authors. 605 pages, illustrated. $22.50. Boston and Toronto: Little, Brown & Co., 1960.

MORFOLOGIA E BIOMETRIA DEI SISTEMI VASCOLARI DEL FEGATO NORMALE E EIRROTICO. By Dott. R. Dòmini. 131 pages, illustrated. Milano: Fondazione D. Ganassini, Edizioni del Premia Ganassini, 1959.